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RESPIRATORY SYNCYTIAL VIRUS REPLICATION INHIBITORS

The present invention is concerned with benzimidazoles and imidazopyridines having antiviral activity, in particular, they have an inhibitory activity on the replication of the respiratory syncytial virus. It further concerns their preparation and compositions comprising them, as well as their use as a medicine.

Human RSV or Respiratory Syncytial Virus is a large RNA virus, member of the family of Paramyxoviridae, subfamily pneumovirinae together with bovine RSV virus. Human RSV is responsible for a spectrum of respiratory tract diseases in people of all ages throughout the world. It is the major cause of lower respiratory tract illness during infancy and childhood. Over half of all infants encounter RSV in their first year of life, and almost all within their first two years. The infection in young children can cause lung damage that persists for years and may contribute to chronic lung disease in later life (chronic wheezing, asthma). Older children and adults often suffer from a (bad) common cold upon RSV infection. In old age, susceptibility again increases, and RSV has been implicated in a number of outbreaks of pneumonia in the aged resulting in significant mortality.

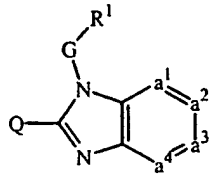
Infection with a virus from a given subgroup does not protect against a subsequent infection with an RSV isolate from the same subgroup in the following winter season. Re-infection with RSV is thus common, despite the existence of only two subtypes, A and B.

Today only three drugs have been approved for use against RSV infection. Ribavirin, a nucleoside analogue, provides an aerosol treatment for serious RSV infection in hospitalized children. The aerosol route of administration, the toxicity (risk of teratogenicity), the cost and the highly variable efficacy limit its use. The other two drugs, RespiGam® and palivizumab, polyclonal and monoclonal antibody immunostimulants, are intended to be used in a preventive way.

Other attempts to develop a safe and effective RSV vaccine have all met with failure thus far. Inactivated vaccines failed to protect against disease, and in fact in some cases enhanced disease during subsequent infection. Life attenuated vaccines have been tried with limited success. Clearly there is a need for an efficacious non-toxic and easy to administer drug against RSV replication.

EP-A-0,005,318 , EP-A-0,099,139 , EP-A-0,145,037 , EP-A-0,144,101 , EP-A-0,151,826 , EP-A-0,151,824 , EP-A-0,232,937 , EP-A-0,295,742 , EP 0,297,661 , EP-A-0,307,014 , WO 92 01697 describe benzimidazole and imidazopyridine substituted piperidine and piperazine derivatives as antihistaminics, antiallergics or serotonine antagonists.

The present invention concerns the use of a compound for the manufacture of a medicament for treating viral infections, wherein the compound is a compound of formula



(I)

a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex and stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);

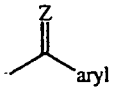
-N=CH-CH=CH- (a-2);

-CH=N-CH=CH- (a-3);

-CH=CH-N=CH- (a-4); or

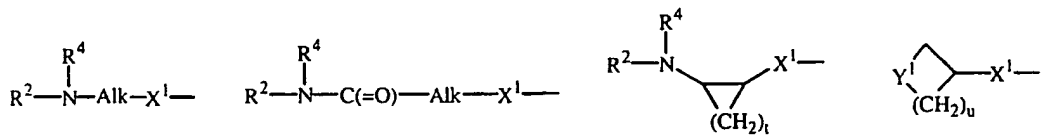
-CH=CH-CH=N- (a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula

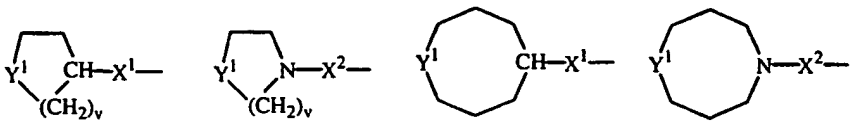


wherein =Z is =O, =CH-C(=O)-$NR^{5a}R^{5b}$, $=CH_2$, =CH-C_{1-6}alkyl, =N-OH or =N-O-C_{1-6}alkyl;

Q is a radical of formula



(b-1) (b-2) (b-3) (b-4)



(b-5) (b-6) (b-7) (b-8)

wherein Alk is C_{1-6}alkanediyl;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl;

t is 2, 3, 4 or 5;

u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8) may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl;

R^1 is a monocyclic heterocycle selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, and isothiazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;

each n independently is 1, 2, 3 or 4;

R^2 is hydrogen, formyl, C_{1-6}alkylcarbonyl, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with $N(R^6)_2$, or C_{1-10}alkyl substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl or arylC_{1-6}alkyloxy;

R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;

R^{5a}, R^{5b}, R^{5c} and R^{5d} each independently are hydrogen or C_{1-6}alkyl; or

R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together form a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;

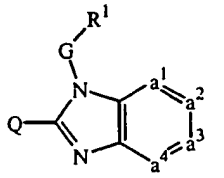
R^6 is hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkyloxy; and

Het is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl.

The present invention also relates to a method of treating warm-blooded animals suffering from or susceptible to viral infections, in particular RSV infection. Said method comprises the administration of a therapeutically effective amount of a compound of formula (I) or a prodrug thereof, a *N*-oxide form, a pharmaceutically acceptable acid or base addition salt, a quaternary amine, a metal complex or a stereochemically isomeric form thereof in admixture with a pharmaceutical carrier.

A further embodiment of the present invention includes the compounds of formula (I')



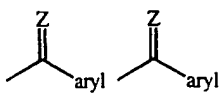
(I')

their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms, wherein

$-a^1=a^2-a^3=a^4-$ represents a radical of formula

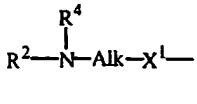
-CH=CH-CH=CH-	(a-1);
-N=CH-CH=CH-	(a-2);
-CH=N-CH=CH-	(a-3);
-CH=CH-N=CH-	(a-4); or
-CH=CH-CH=N-	(a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula

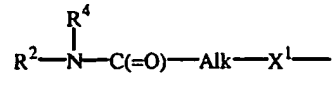


wherein =Z is =O, =CH-C(=O)-$NR^{5a}R^{5b}$, $=CH_2$, =CH-C_{1-6}alkyl, =N-OH or =N-O-C_{1-6}alkyl;

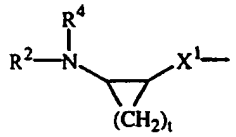
Q is a radical of formula



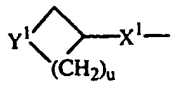
(b-1)



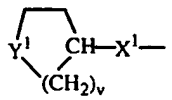
(b-2)



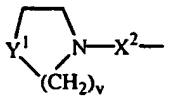
(b-3)



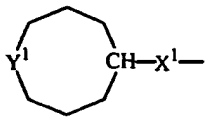
(b-4)



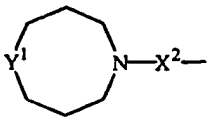
(b-5)



(b-6)



(b-7)



(b-8)

wherein Alk is C_{1-6}alkanediyl;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl;

t is 2, 3, 4 or 5;

u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8) may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl;

R^1 is a monocyclic heterocycle selected from pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, imidazolyl and pyrazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkyl-carbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;

each n independently is 1, 2, 3 or 4;

R^2 is hydrogen, formyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with $N(R^6)_2$, or C_{1-10}alkyl substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl or arylC_{1-6}alkyloxy;

R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;

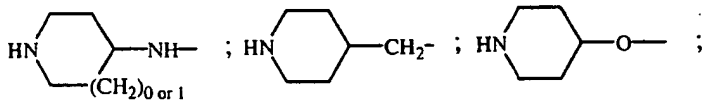
R^{5a}, R^{5b}, R^{5c} and R^{5d} each independently are hydrogen or C_{1-6}alkyl; or

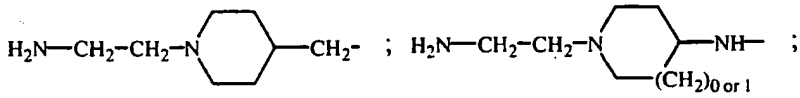
R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together form a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;

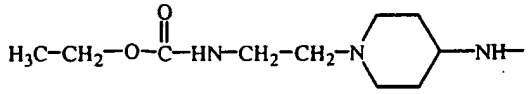
R^6 is hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;

provided that when G is methylene, and R^1 is 2-pyridyl, 3-pyridyl, 6-methyl-2-pyridyl, 2-pyrazinyl or 5-methyl-imidazol-4-yl, and $-a^1=a^2-a^3=a^4-$ is –CH=CH-CH=CH- or -N=CH-CH=CH-, then Q is other than







Yet another embodiment of the present invention includes the following group of compounds

2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-5-chloro-7-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride tetrahydrate;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2,4-dimethyl-5-oxazolyl)methyl]-*1H*-benzimidazol-2-amine;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2,5-dimethyl-4-oxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate;

4-[[3-[[5-(methoxymethyl)-2-furanyl]methyl]-3*H*-imidazo[4,5-b]pyridine-2-yl]methyl]-1-piperidineetanamine;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(5-methyl-3-isoxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate;
N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methyl-5-oxazolyl)methyl]-*1H*-benzimidazol-2-amine monohydrate;
N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methyl-5-oxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate;
N-[1-(2-aminoethyl)-4-piperidinyl]-3-[(2,4-dimethyl-5-oxazolyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine;
4-[[3-[(2-methyl-5-oxazolyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]methyl]-1-piperazineethanamine;
N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-thiazolylmethyl)-*1H*-benzimidazol-2-amine;
N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(5-phenyl-1,2,4-oxadiazol-3-yl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride;
5-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino-*1H*-benzimidazol-1-yl]methyl-2-oxazolemethanol tetrahydrochloride dihydrate;
N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(3-methyl-5-isoxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate;
4-[[1-[[2-(dimethylamino)-4-thiazolyl]methyl]-*1H*-benzimidazol-2-yl]methyl]-1-piperidineethanamine tetrahydrochloride monohydrate 2-propanolate (1:1);
ethyl 5-[[2-[[1-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl]methyl]-2-methyl-4-oxazolecarboxylate;
4-[[1-[(2-methyl-4-thiazolyl)methyl]-*1H*-benzimidazol-2-yl]methyl]-1-piperidineetahnamine;
N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methyl-3-furanyl)methyl]-*1H*-benzimidazol-2-amine;
ethyl 4-[[3-[(3-hydroxy-6-methyl-2-pyridinyl)methyl]-7-methyl-3H-imidazo[4,5-b]pyridine-2-yl]amino]-1-piperidinecarboxylate;
1,1-dimethylethyl 4-[[1-[[3-[2-(dimethylamino)ethoxy]-6-methyl-2-pyridinyl]methyl]-*1H*-benzimidazol-2-yl]amino-1-piperidinecarboxylate;
ethyl 4-[[1-[(3-amino-2-pyridinyl)methyl]-*1H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate; and
N-[1-(6-methyl-2-pyridinyl)-*1H*-benzimidazol-2-yl]-1-(3-pyridinylcarbonyl)-4-piperidinamine.

the prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms thereof.

Said group of compounds will be referred to hereinafter as the compounds of group (I'').

The term prodrug as used throughout this text means the pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p. 13-15) describing prodrugs generally, is hereby incorporated.

As used herein C_{1-3}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 3 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl and the like; C_{1-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as the group defined for C_{1-3}alkyl and butyl and the like; C_{2-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 2 to 4 carbon atoms such as ethyl, propyl, 1-methylethyl, butyl and the like; C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylbutyl and the like; C_{1-9}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 9 carbon atoms such as the groups defined for C_{1-6}alkyl and heptyl, octyl, nonyl, 2-methylhexyl, 2-methylheptyl and the like; C_{1-10}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 10 carbon atoms such as the groups defined for C_{1-9}alkyl and decyl, 2-methylnonyl and the like. C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{2-5}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 2 to 5 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,2-propanediyl, 2,3-butanediyl, 1,5-pentanediyl and the like, C_{2-5}alkanediyl is substituted on C_{1-10}alkyl as provided for in the definition of R^2, it is meant to be substituted on one carbon atom thus forming a spiro moiety; C_{1-4}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C_{1-6}alkanediyl is meant to include C_{1-4}alkanediyl and the higher homologues thereof having from 5 to 6 carbon atoms such as, for example, 1,5-pentanediyl, 1,6-hexanediyl and the like; C_{1-10}alkanediyl is meant to include C_{1-6}alkanediyl and the higher homologues thereof having from 7 to 10 carbon atoms such as, for example, 1,7-heptanediyl, 1,8-octanediyl, 1,9-nonanediyl, 1,10-decanediyl and the like.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom. The term (=N-OH) forms a hydroxylimine moiety when attached to a carbon atom.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhaloC_{1-6}alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-6}alkyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl. In case more than one halogen atoms are attached to an alkyl group within the definition of polyhaloC_{1-4}alkyl, they may be the same or different.

When any variable (e.g. aryl, R^2, R^3, R^4, R^{5a}, R^{5b} etc.) occurs more than one time in any constituent, each definition is independent.

It will be appreciated that some of the compounds of formula (I), (I') or the compounds of group (I'') and their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds of formula (I), (I') or the compounds of group (I''), and their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I), (I') or the compounds of group (I'') and their prodrugs, *N*-oxides, salts, solvates, quaternary amines, metal complexes substantially free, *i.e.* associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1% of the other isomers. Stereochemically isomeric forms of the compounds of formula (I), (I') or the compounds of group (I'') are obviously intended to be embraced within the scope of this invention.

As used hereinafter the terms trans, cis, R or S are well-known by the person skilled in the art.

For some of the compounds of formula (I), (I') or the compounds of group (I''), their prodrugs, *N*-oxides, salts, solvates, quaternary amines or metal complexes and the intermediates used in the preparation thereof, the absolute stereochemical configuration was not experimentally determined. In these cases the stereoisomeric form which was first isolated is designated as "A" and the second as "B", without further reference to the actual stereochemical configuration. However, said "A" and "B" stereoisomeric forms can be unambiguously characterized by for instance their optical rotation in case "A" and "B" have an enantiomeric relationship. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction. In case "A" and "B" are stereoisomeric mixtures, they can be further separated whereby the respective first fractions isolated are designated "A1" and "B1" and the second as "A2" and "B2", without further reference to the actual stereochemical configuration.

For therapeutic use, salts of the compounds of formula (I), (I') or the compounds of group (I'') are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I), (I') or the compounds of group (I'') are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic (i.e. hydroxybutanedioic acid), tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I), (I') or the compounds of group (I'') containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I), (I') or the compounds of group (I'') as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I), (I') or the compounds of group (I'') are able to form by reaction between a basic nitrogen of a compound of formula (I), (I') or the compounds of group (I'') and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyliodide or benzyliodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

It will be appreciated that the compounds of formula (I), (I') or the compounds of group (I'') may have metal binding, chelating, complexating properties and therefore may exist as metal complexes or metal chelates. Such metalated derivatives of the compounds of formula (I), (I') or the compounds of group (I'') are intended to be included within the scope of the present invention.

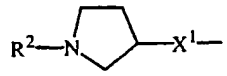
Some of the compounds of formula (I), (I') or the compounds of group (I'') may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

A special group of compounds are those compounds of formula (I) or (I') wherein one or more of the following restrictions apply:

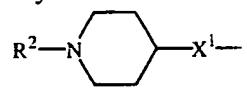
- Q is a radical of formula (b-1), (b-3), (b-4), (b-5), (b-6), (b-7) or (b-8);
- X^2 is a direct bond, CH_2 or C(=O);

- R^1 is a monocyclic heterocycle selected from pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, imidazolyl and pyrazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkyl-carbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;
- R^2 is hydrogen, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with NHR^6, or C_{1-10}alkyl substituted with NHR^6 and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;
- R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy or arylC_{1-6}alkyl;
- R^6 is hydrogen, C_{1-4}alkyl, formyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl.

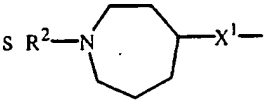
A special group of compounds are those compounds of formula (I') wherein the following restrictions apply :

when Q is 

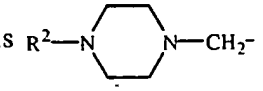
wherein X^1 is NR^4, O, S, S(=O), S(=O)$_2$, CH_2, C(=O), C(=CH_2) or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl;

when Q is 

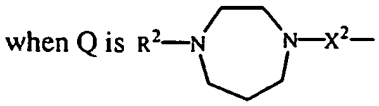
wherein X^1 is NR^4, O, S, S(=O), S(=O)$_2$, CH_2, C(=O), C(=CH_2) or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyridyl substituted with 1 or 2 C_{1-6}alkyloxy, pyrazinyl, pyrrolyl, pyrrolyl substituted with C_{1-6}alkyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl;

when Q is 

wherein X^1 is NR^4, O, S, S(=O), S(=O)$_2$, CH_2, C(=O), C(=CH_2) or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl;

when Q is 

then R^1 is other than pyridyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl;

when Q is 

wherein X^2 is CH_2 or a direct bond, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

Or a special group of compounds are those compounds of formula (I') wherein one of the following applies :

Q is a radical of formula (b-1); (b-2); (b-3); (b-5); (b-6); (b-7); (b-8); (b-4) wherein u is 1,3,4 or 5; or (b-4) wherein u is 2, wherein Y^1 is $-CH(NR^2R^4)-$, wherein X^1 is CH(OH), $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2, and wherein R^1 is pyridyl or imidazolyl, each of said heterocycles substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, $-C(=O)-NR^{5c}R^{5d}$, $HO(-CH_2-CH_2-O)_n-$, halo$(-CH_2-CH_2-O)_n-$, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$, arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$ and mono-or di(C_{1-6}alkyl)amino$(-CH_2-CH_2-O)_n-$, or each of said heterocycles substituted with, where possible 2, 3 or 4 C_{1-6}alkyl groups; or wherein R^1 is pyrimidinyl or pyrazinyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, $-C(=O)-NR^{5c}R^{5d}$, $HO(-CH_2-CH_2-O)_n-$, halo$(-CH_2-CH_2-O)_n-$, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$, arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$ and mono-or di(C_{1-6}alkyl)amino$(-CH_2-CH_2-O)_n-$; or wherein R^1 is pyrrolyl or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, $-C(=O)-NR^{5c}R^{5d}$, $HO(-CH_2-CH_2-O)_n-$, halo$(-CH_2-CH_2-O)_n-$,

C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or

Q is a radical of formula (b-1); (b-2); (b-3); (b-4); (b-6); (b-7); (b-8); (b-5) wherein v is 3; or (b-5) wherein v is 2, wherein Y^1 is –CH(NR^2R^4)-, wherein X^1 is CH(OH), $CH(OCH_3)$, $CH(SCH_3)$, CH($NR^{5a}R^{5b}$), CH_2-NR^4 or NR^4-CH_2, and wherein R^1 is pyrrolyl or imidazolyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-, or each of said heterocycles being substituted with, where possible 2, 3 or 4 C_{1-6}alkyl groups; or wherein R^1 is pyridyl being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-, or pyridyl being substituted with, 2, 3 or 4 C_{1-6}alkyl groups or 3 or 4 C_{1-6}alkyloxy groups; or wherein R^1 is pyrazinyl being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkyl-carbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or wherein R^1 is pyridazinyl, pyrimidinyl or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkyl-carbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$ HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-

$O)_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or

Q is a radical of formula (b-1); (b-2); (b-3); (b-4); (b-6); (b-7); (b-8); (b-5) wherein v is 2; or (b-5) wherein v is 3, wherein Y^1 is –CH(NR^2R^4)-, wherein X^1 is CH(OH), $CH(OCH_3)$, $CH(SCH_3)$, CH($NR^{5a}R^{5b}$), CH_2-NR^4 or NR^4-CH_2, and wherein R^1 is pyridyl or imidazolyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-, or each of said heterocycles being substituted with, where possible 2, 3 or 4 C_{1-6}alkyl groups; or wherein R^1 is pyrimidinyl or pyrazinyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or wherein R^1 is pyrrolyl or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or

Q is a radical of formula (b-1); (b-2); (b-3); (b-4); (b-5); (b-7); (b-8); (b-6) wherein v is 3; or (b-6) wherein v is 2, wherein Y^1 is –CH(NR^2R^4)-, wherein X^2 is a direct bond or C(=O), or X^2 is a direct bond, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl, wherein R^1 is pyridyl, pyrimidinyl or pyrazinyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino,

cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or wherein R^1 is imidazolyl being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkyl-carbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-, or imidazolyl being substituted with 2 or 3 C_{1-6}alkyl groups; or wherein R^1 is pyridazinyl, pyrrolyl, or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or

Q is a radical of formula (b-1); (b-2); (b-3); (b-4); (b-5); (b-7); (b-8); (b-6) wherein v is 2; or (b-6) wherein v is 3, Y^1 is –CH(NR^2R^4)-, wherein X^2 is C(=O) or X^2 is C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl, and wherein R^1 is pyridyl or imidazolyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-, or each of said heterocycles being substituted with, where possible 2, 3 or 4 C_{1-6}alkyl groups; or wherein R^1 is pyrimidinyl or pyrazinyl, each of said heterocycles being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio,

C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkyl-carbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-; or wherein R^1 is pyrrolyl or pyrazolyl, each of said heterocycles optionally being substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkyl-carbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-.

Preferred compounds are

(±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-7-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride monohydrate;

2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl]methyl-3-pyridinol;

(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(1,4-dimethyl-*1H*-imidazol-5-yl)methyl]-*1H*-benzimidazol-2-amine monohydrate;

(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(6-methyl-2-pyridinyl)methyl]-*1H*-benzimidazol-2-amine;

(±)-2-[[2-[(3-amino-2-hydroxypropyl)amino]-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[[3-(2-ethoxyethoxy)-6-methyl-2-pyridinyl]methyl]-*1H*-benzimidazol-2-amine tetrahydrochloride dihydrate;

(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-chloro-1,4-dimethyl-*1H*-imidazol-5-yl)methyl]-*1H*-benzimidazol-2-amine;

(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(2-chloro-1,4-dimethyl-*1H*-imidazol-5-yl)methyl]-*1H*-benzimidazol-2-amine;

(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-methyl-1-[(6-methyl-2-pyridinyl)methyl]-*1H*-benzimidazol-2-amine;

(±)-*N*-[1-(2-aminopropyl)-4-piperidinyl]-1-[(3,5,6-trimethylpyrazinyl)methyl]-*1H*-benzimidazol-2-amine tetrahydrochloride trihydrate;

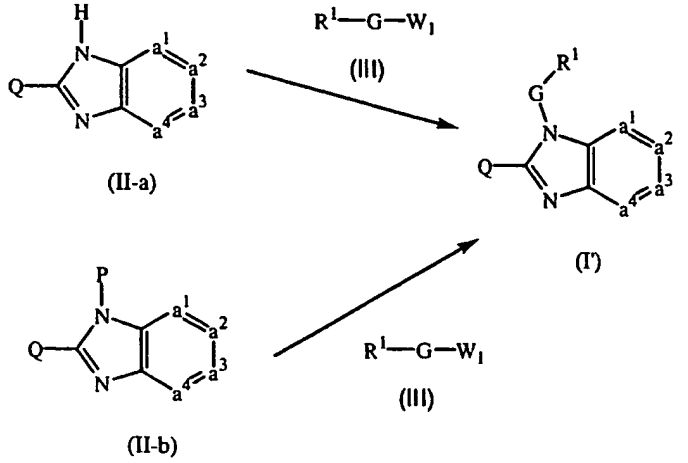
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(3,5,6-trimethylpyrazinyl)methyl]-*1H*-benzimidazol-2-amine;

N-[1-(2-aminoethyl)-4-piperidinyl]-1-[[3-(2-chloroethoxy)-6-methyl-2-pyridinyl]methyl]-*1H*-benzimidazol-2-amine trihydrochloride dihydrate;
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[3-amino-2-pyridinyl)methyl]-*1H*-benzimidazol-2-amine tetrahydrochloride trihydrate;
the prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms thereof.

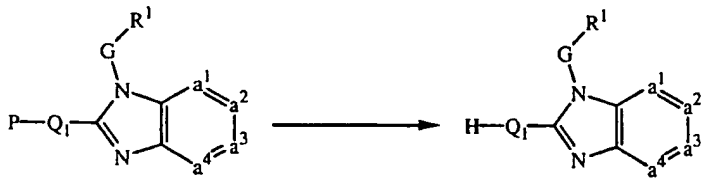
Most preferred are
2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride;
(±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-7-methyl-3*H*-imidazo[4,5-b]pyridin-3-yl]methyl]-6-methyl-3-pyridinol;
2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-6-chloro-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride 2-propanolate (1:1);
(±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol;
(±)-2-[[2-[[1-(2-aminopropyl)-4-piperidinyl]amino]-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride trihydrate;
2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-7-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride dihydrate;
2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-6-bromo-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride;
2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride monohydrate;
(±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol; and
(±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-[(6-methyl-2-pyridinyl)-methyl]-*1H*-benzimidazol-2-amine.
the prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms thereof.

In general, compounds of formula (I') can be prepared by reacting an intermediate of formula (II-a) or (II-b), wherein P represents a protecting group, such as, for example C_{1-4}alkyloxycarbonyl, or those protecting groups mentioned in Chapter 7 of 'Protective Groups in Organic Synthesis' by T Greene and P. Wuyts (John Wiley & Sons Inc., 1991), with an intermediate of formula (III), wherein W_1 is a suitable leaving group, such as a halo atom, e.g. chloro, bromo, in the presence of a suitable base, such as, e.g.

sodium hydride, disodium carbonate. Said reaction can be performed in a reaction-inert solvent, such as *N,N*-dimethylformamide.



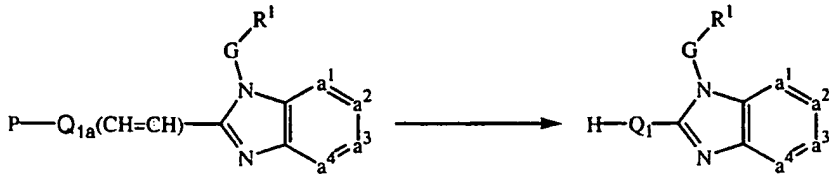
Compounds of formula (I') wherein, in the definition of Q, R^2 or at least one R^6 substituent is hydrogen, said Q being represented by H-Q_1, and said compounds being represented by formula (I'-a), can be prepared by deprotecting an intermediate of formula (IV) wherein P represents a protecting group, for example C_{1-4}alkyloxycarbonyl, benzyl, or those protecting groups mentioned in Chapter 7 of 'Protective Groups in Organic Synthesis' by T Greene and P. Wuyts (John Wiley & Sons Inc., 1991).



When P represents, for example, C_{1-4}alkyloxycarbonyl, said deprotection reaction can be performed by, for example, acidic hydrolysis in the presence of a suitable acid, such as hydrobromic, hydrochloric, sulfuric, acetic, or trifluoroacetic acid or a mixture of said acids, or by alkaline hydrolysis in the presence of a suitable base, such as, for example potassium hydroxide, in a suitable solvent such as water, alcohol, a mixture of water-alcohol, methylene chloride. Suitable alcohols are methanol, ethanol, 2-propanol, 1-butanol and the like. In order to enhance the rate of the reaction, it is advantageous to heat the reaction mixture, in particular up to the reflux temperature. Alternatively, when P represents, for example, benzyl, the deprotection reaction can be performed by catalytic hydrogenation in the presence of hydrogen and an appropriate catalyst in a reaction-inert solvent. A suitable catalyst in the above reaction is, for

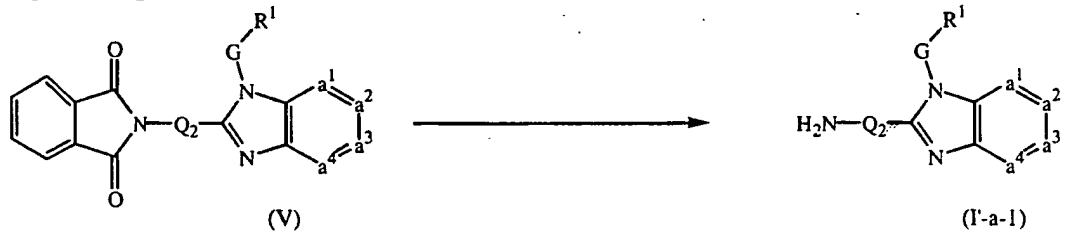
example, platinum-on-charcoal, palladium-on-charcoal, and the like. An appropriate reaction-inert solvent for said reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like, an ester, e.g. ethylacetate and the like, an acid, e.g. acetic acid and the like.

The catalytic hydrogenation reaction described above can also be used to prepare a compound of formula (I'-a) by deprotecting and reducing an intermediate of formula (IV) wherein Q_1 comprises an unsaturated bond, said Q_1 being represented by $Q_{1a}(CH=CH)$, and said intermediate being represented by formula (IV-a).



(IV-a) (I'-a)

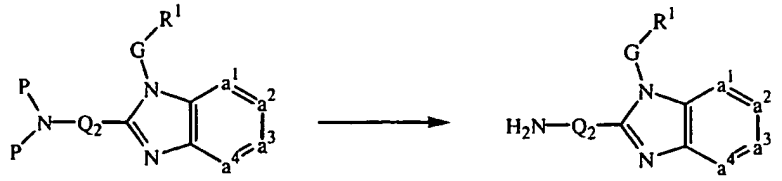
Compounds of formula (I') wherein, in the definition of Q, both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, said Q being represented by H_2N-Q_2, and said compounds being represented by formula (I'-a-1), can also be prepared by deprotecting an intermediate of formula (V).



(V) (I'-a-1)

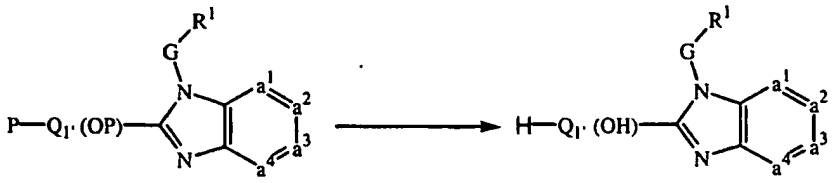
Said deprotection reaction can be performed in the presence of a suitable base such as, for example hydrazine, or in the presence of a suitable acid, such as hydrochloric acid and the like, in a suitable solvent, such as an alcohol, acetic acid and the like.

Compounds of formula (I'-a-1) can also be prepared by deprotecting an intermediate of formula (VI) according to the procedure described for the preparation of compounds of formula (I'-a).

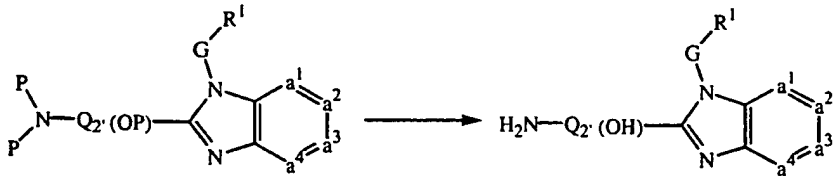


(VI) (I'-a-1)

Compounds of formula (I'-a) or (I'-a-1), wherein Q_1 or Q_2 comprise a hydroxy substituent, said Q_1 or Q_2 being represented by Q_1-(OH) or Q_2-(OH), and said compounds being represented by formula (I'-a-2) or (I'-a-1-1), can be prepared by deprotecting an intermediate of formula (VII) or (VIII) as described hereinabove for the preparation of compounds of formula (I'-a).

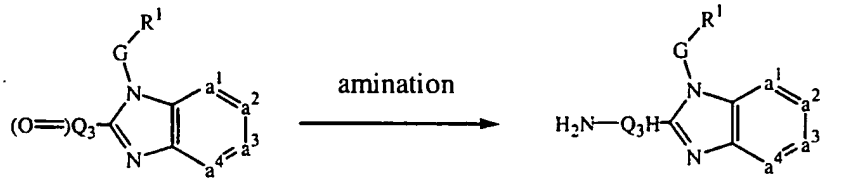


(VII) (I'-a-2)



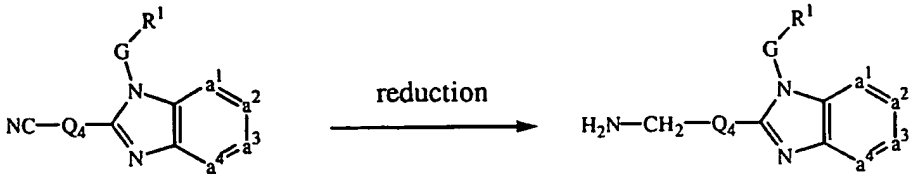
(VIII) (I'-a-1-1)

Compounds of formula (I') wherein, in the definition of Q, both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6 or R^2 and R^4 substituents, contains at least one hydrogen, said Q being represented by H_2N-Q_3H, and said compounds being represented by formula (I'-a-1-2) can also be obtained by reductive amination of intermediates of formula (IX) in the presence of a suitable amination reagent, such as, for example, ammonia, hydroxylamine, or benzylamine, and in the presence of a suitable reducing agent, e.g. hydrogen, and an appropriate catalyst. An appropriate catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, rhodium-on-Al_2O_3, and the like, optionally in the presence of a catalyst poison, such as a thiophene solution. A suitable reaction-inert solvent for the above reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like.



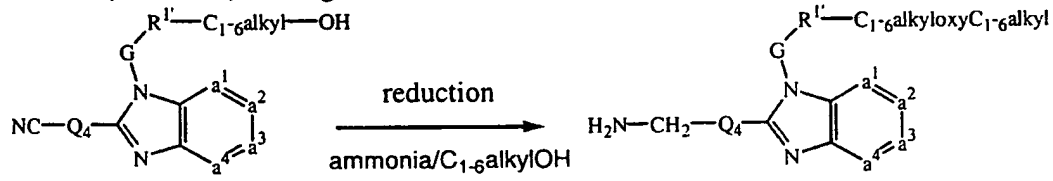
(IX) (I'-a-1-2)

Compounds of formula (I'), wherein Q comprises a $-CH_2NH_2$ moiety, said Q being represented by $H_2N-CH_2-Q_4$, and said compounds being represented by formula (I'-a-1-3) can be prepared by reducing an intermediate of formula (X).



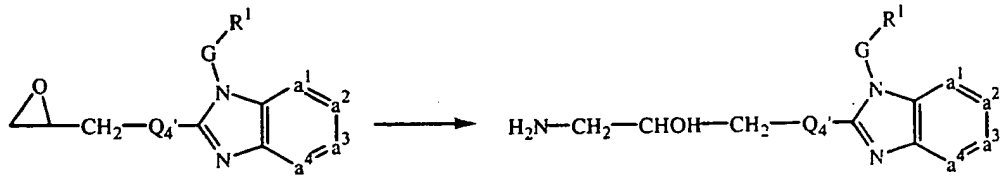
(X) (I'-a-1-3)

Said reduction can be performed with a suitable reducing agent, such as lithium aluminium hydride or hydrogen, optionally in the presence of a suitable catalyst, such as Raney Nickel. A suitable solvent for the above reaction is, for example, tetrahydrofuran, or a solution of ammonia in an alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like. Said reduction reaction performed in a solution of ammonia in an alcohol can also be used to prepare compounds of formula (I'-a-1-3), wherein R^1 is substituted with $C_{1-6}alkyloxyC_{1-6}alkyl$, said R^1 being represented by $R^{1'}$-$C_{1-6}alkyloxyC_{1-6}alkyl$, and said compounds being represented by formula (I'-a-1-3-1) starting from an intermediate of formula (X-a).



(X-a) (I'-a-1-3-1)

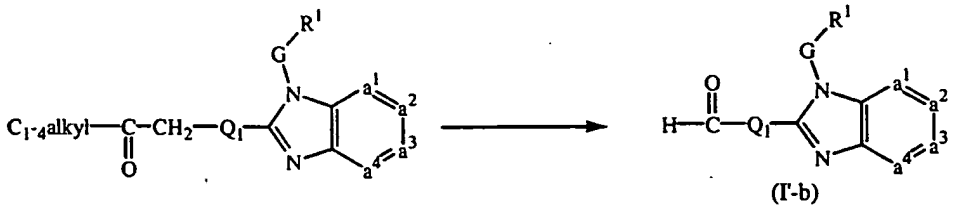
Compounds of formula (I'), wherein Q comprises a $-CH_2-CHOH-CH_2-NH_2$ moiety, said Q being represented by $H_2N-CH_2-CHOH-CH_2-Q_4$', and said compounds being represented by formula (I'-a-1-3-2), can be prepared by reacting an intermediate of formula (XI) with ammonia in the presence of a suitable reaction-inert solvent, such as an alcohol, e.g. methanol.



(XI) (I'-a-1-3-2)

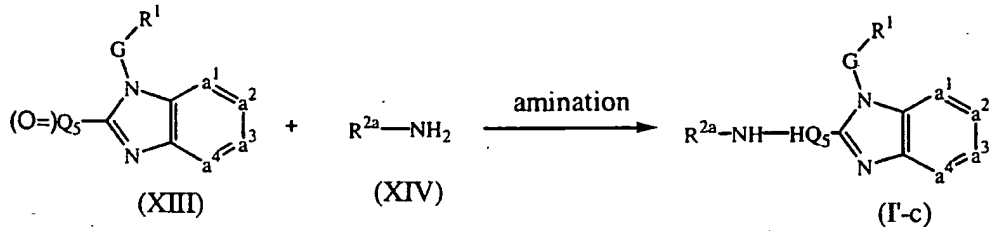
Compounds of formula (I'), wherein, in the definition of Q, R^2 or one R^6 substituent is formyl, said Q being represented by H-C(=O)-Q_1, and said compounds being

represented by formula (I'-b), can be prepared by reacting an intermediate of formula (XII) with formic acid, formamide and ammonia.



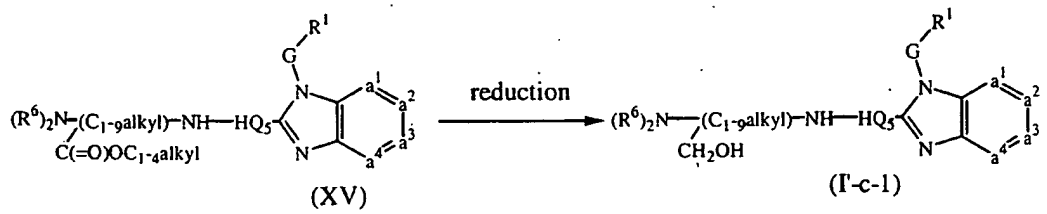
(XII) (I'-b)

Compounds of formula (I'), wherein, in the definition of Q, R^2 is other than hydrogen, said R^2 being represented by R^{2a}, R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, said Q being represented by R^{2a}-NH-HQ_5, and said compounds being represented by formula (I'-c), can be prepared by reductive amination of an intermediate of formula (XIII) with an intermediate of formula (XIV) in the presence of a suitable reducing agent, such as hydrogen, and a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal, and the like. A suitable reaction-inert solvent for the above reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like.



(XIII) (XIV) (I'-c)

Compounds of formula (I'-c), wherein R^{2a} represents C_{1-10}alkyl substituted with $N(R^6)_2$ and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, said R^{2a} being represented by $[(C_{1-9}alkyl)CH_2OH]$-$N(R^6)_2$, and said compounds being represented by formula (I'-c-1), can be prepared by reducing an intermediate of formula (XV) in the presence of a suitable reducing agent, such as lithium aluminium hydride, in a suitable reaction-inert solvent, such as tetrahydrofuran.

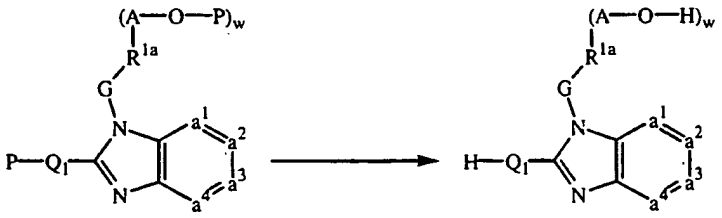


(XV) (I'-c-1)

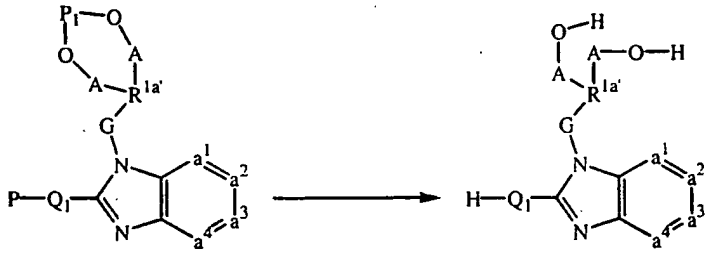
Compounds of formula (I') wherein, in the definition of Q, R^2 or one R^6 substituent is hydrogen, said Q being represented by H-Q_1, and wherein R^1 is a monocyclic heterocycle substituted with 1 or more substituents selected from hydroxy,

hydroxyC_{1-6}alkyl, or HO(-CH_2-CH_2-O)$_n$-, said substituents being represented by formula A-OH, said R^1 being represented by R^{1a}-(A-OH)$_w$, with w being the amount of substituents on R^{1a} ranging from 1 to 4, and said compounds being represented by formula (I'-d), can be prepared by deprotecting an intermediate of formula (XVI) with a suitable acid, such as hydrochloric acid and the like, optionally in the presence of a suitable solvent, such as an alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like.

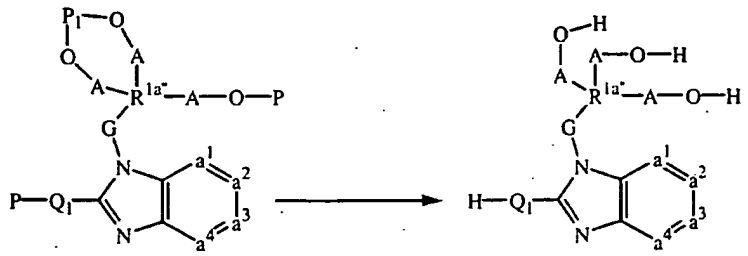
Alternatively, one protecting group may also protect more than one substituent of R^{1a}, said protecting group being represented by P_1, as represented by formula (XVI-a). The two ways of protecting the substituents of R^{1a}, i.e. with a separate, as in formula (XVI), or a combined, as in formula (XVI-a), protecting group, may also be combined in the same intermediate, as represented by formula (XVI-b).



(XVI) (I'-d)



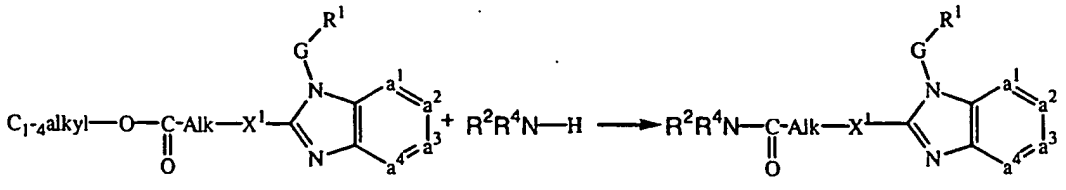
(XVI-a) (I'-d-1)



(XVI-b) (I'-d-2)

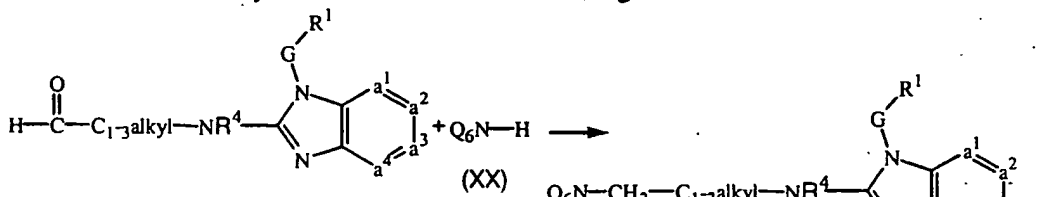
Compounds of formula (I'), wherein Q is a radical of formula (b-2), said compounds being represented by formula (I'-e), can be prepared by reacting an intermediate of formula (XVII) with an intermediate of formula (XVIII) in the presence of sodium

cyanide and a suitable reaction-inert solvent, such as an alcohol, e.g. methanol and the like.



(XVII) (XVIII) (I'-e)

Compounds of formula (I'), wherein in the definition of Q, X^2 is C_{2-4}alkyl-NR^4, said Q being represented by Q_6N-CH_2-C_{1-3}alkyl-NR^4, and said compounds being represented by formula (I'-p), can be prepared by reacting an intermediate of formula (XIX) with an intermediate of formula (XX) in the presence of isopropyl titanate (IV) and a suitable reducing agent, such as $NaBH_3CN$, and in the presence of a suitable reaction-inert solvent, such as methylene chloride or an alcohol, e.g. ethanol.

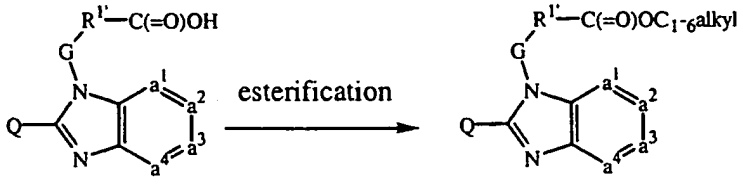


(XIX) (XX) (I'-p)

ompounds of formula (I') may be converted into each other following art-known functional group transformation reactions, comprising those described hereinafter.

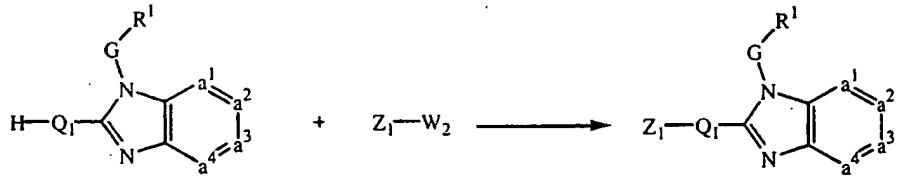
The compounds of formula (I') may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I') with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Compounds of formula (I'), wherein R^1 is monocyclic heterocycle substituted with C_{1-6}alkyloxycarbonyl, said R^1 being represented by $R^{1'}$-C(=O)OC_{1-6}alkyl, and said compounds being represented by formula (I'-f), can be prepared by esterification of a compound of formula (I'-g) in the presence of a suitable alcohol, e.g. methanol, ethanol, propanol, butanol, pentanol, hexanol and the like, and in the presence of a suitable acid, such as hydrochloric acid and the like.



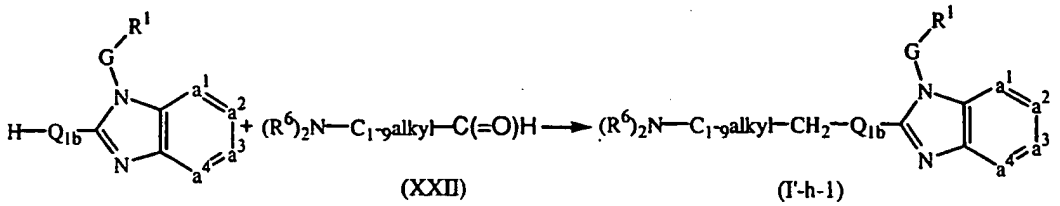
(I'-g) (I'-f)

Compounds of formula (I'-a) may be converted into compounds of formula (I'), wherein, in the definition of Q, R^2 or at least one R^6 substituent is other than hydrogen, said R^2 or R^6 being represented by Z_1, said Q being represented by Z_1-Q_1, and said compounds being represented by formula (I'-h), by reaction with a reagent of formula (XXI), wherein W_2 is a suitable leaving group, such as a halo atom, e.g. bromo, or 4-methylbenzenesulphonate, in the presence of a suitable base, such as, for example disodium carbonate, dipotassium carbonate, sodium hydroxide and the like, in a reaction-inert solvent, e.g. 3-methyl-2-butanone, acetonitrile, *N*,*N*-dimethylformamide.



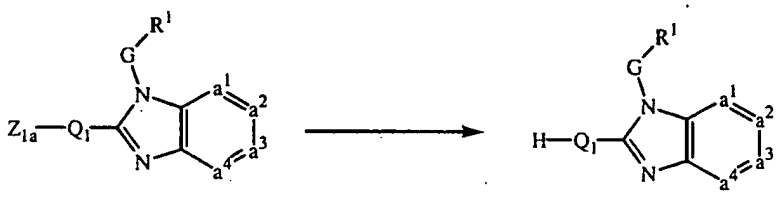
(I'-a) (I'-h)

Compounds of formula (I'-h), wherein, in the definition of Z_1, R^2 is CH_2-C_{1-9}alkyl substituted with $N(R^6)_2$, said compounds being represented by formula (I'-h-1), can also be prepared by reacting a compound of formula (I'-a) wherein, in the definition of H-Q_1, R^2 is hydrogen, said H-Q_1 being represented by H-Q_{1b}, and said compounds being represented by formula (I'-a-3), with an intermediate of formula (XXII), in the presence of a suitable reducing agent, such as sodium cyanoborohydride, in a suitable reaction-inert solvent, such as an alcohol.



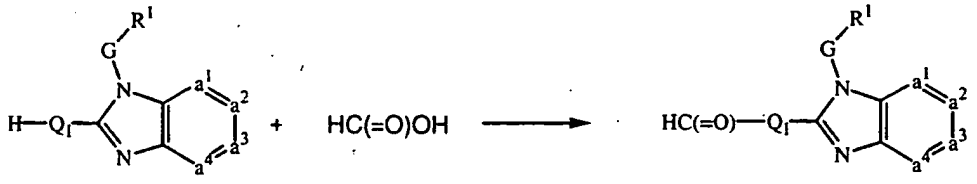
(I'-a-3) (XXII) (I'-h-1)

Compounds of formula (I'-h), wherein Z_1 comprises formyl, C_{1-6}alkylcarbonyl, or C_{1-6}alkyloxycarbonyl, said Z_1 being represented by Z_{1a}, and said compounds being represented by formula (I'-h-2), can be converted into compounds of formula (I'-a), by acidic hydrolysis in the presence of a suitable acid, such as hydrobromic, hydrochloric, sulfuric, acetic, or trifluoroacetic acid or a mixture of said acids, or by alkaline hydrolysis in the presence of a suitable base, such as, for example potassium hydroxide, in a suitable solvent such as water, alcohol, a mixture of water-alcohol, methylene chloride. Suitable alcohols are methanol, ethanol, 2-propanol, 1-butanol, sec. butanol and the like. In order to enhance the rate of the reaction, it is advantageous to work at elevated temperatures.



(I'-h-2) (I'-a)

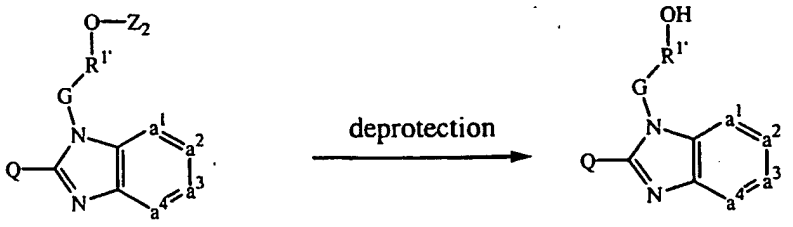
Compounds of formula (I'-b) can be prepared by reacting a compound of formula (I'-a) with formic acid.



(I'-a) (I'-b)

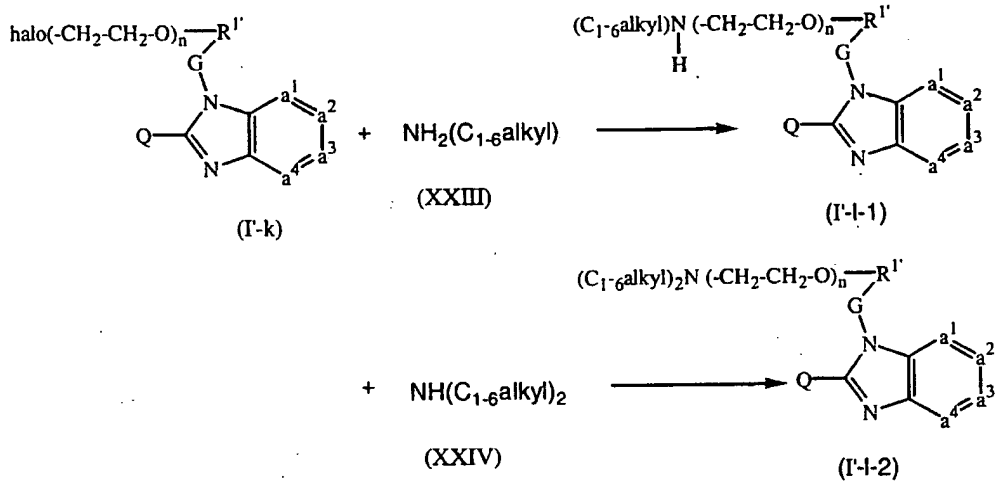
Compounds of formula (I') wherein R^1 is monocyclic heterocycle substituted with hydroxy, said R^1 being represented by HO-$R^{1'}$, and said compounds being represented by formula (I'-i), can be prepared by deprotecting a compound of formula (I'-j), wherein R^1 is monocyclic heterocycle substituted with C_{1-6}alkyloxy or arylC_{1-6}alkyloxy, said C_{1-6}alkyl or arylC_{1-6}alkyl being represented by Z_2, and said R^1 being represented by Z_2-O-$R^{1'}$. Said deprotection can be performed in a reaction-inert solvent, such as, for

example methylene chloride, in the presence of a suitable deprotecting agent, e.g. tribromoborane.



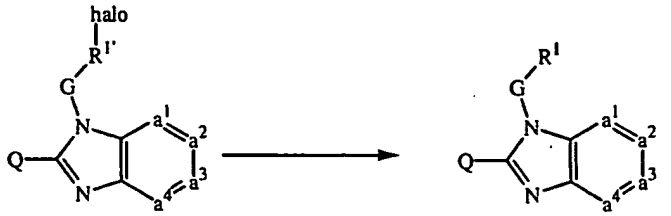
(I'-j) (I'-i)

Compounds of formula (I') wherein R^1 is monocyclic heterocycle substituted with halo(-CH_2-CH_2-O)$_n$, said compounds being represented by formula (I'-k), can be converted into a compound of formula (I'-l-1) or (I'-l-2) by reaction with the appropriate amine of formula (XXIII) or (XXIV) in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



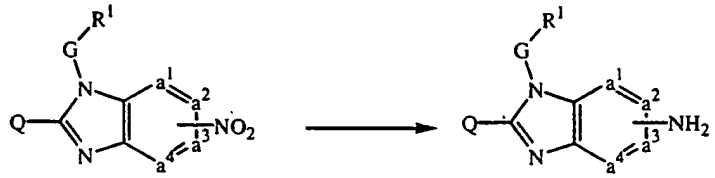
(I'-k) (I'-l-1) (I'-l-2)

Compounds of formula (I'), wherein R^1 is monocyclic heterocycle substituted with halo, said compounds being represented by formula (I'-m) can be converted into compounds of formula (I') by reaction with 1-butanethiol in the presence of palladium-on-charcoal and CaO in a suitable reaction-inert solvent, such as tetrahydrofuran.



(I'-m) (I')

Compounds of formula (I') wherein a hydrogen atom in the radicals of formula (a-1), (a-2), (a-3), (a-4) or (a-5) is replaced by nitro, said compounds being represented by formula (I'-n) may be reduced to a compound of formula (I'-o) in the presence of a suitable reducing agent, such as hydrogen, in the presence of a suitable catalyst, such as platinum-on-charcoal, and optionally in the presence of a suitable catalyst poison, e.g. a thiophene solution. The reaction may be performed in a suitable reaction-inert solvent, such as an alcohol.



(I'-n) (I'-o)

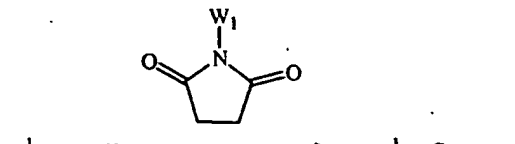
The reactions described hereinabove for the preparation of the compounds of formula (I') can also be used to prepare the compounds of the group (I'').

In the following paragraphs, there are described several methods of preparing the intermediates in the foregoing preparations. A number of intermediates and starting materials are commercially available or are known compounds which may be prepared according to conventional reaction procedures generally known in the art or analogous to the procedures described in EP-A-0,005,318 , EP-A-0,099,139 , EP-A-0,151,824 , EP-A-0,151,826 , EP-A-0,232,937 , EP-A-0,295,742 , EP-A-0,297,661 , EP-A-0,539,420 , EP-A-0,539,421 , US 4,634,704 , US 4,695,569.

In the foregoing and the following preparations, the reaction mixture is worked up following art-known methods and the reaction product is isolated and, if necessary, further purified.

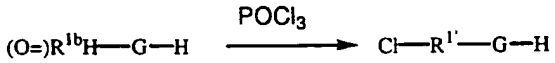
Intermediates of formula (III) can be prepared by reacting an intermediate of formula (XXV) with a suitable leaving group, i.e. W_1, introducing agent, e.g. 1-halo-

2,5-pyrrolidinedione, in the presence of dibenzoyl peroxide, in a reaction-inert solvent, e.g. tetrachloromethane.



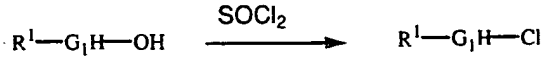
(XXV) (III)

Intermediates of formula (XXV), wherein R^1 is monocyclic heterocycle substituted with chloro, said R^1 being represented by Cl-$R^{1'}$ and said intermediates being represented by formula (XXV-a), can be prepared by reacting an intermediate of formula (XXVI), wherein (O=)R^{1b}H is defined as a carbonyl derivative of $R^{1'}$ wherein one carbon or nitrogen, adjacent to the carbonyl, carries at least one hydrogen, with phosphorus oxychloride. Intermediates of formula (XXVI) may also react as their enol tautomeric forms.



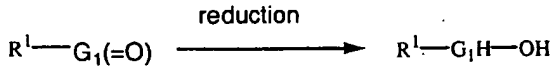
(XXVI) (XXV-a)

Intermediates of formula (III) wherein W_1 is chloro, which is attached to a carbon atom carrying at least one hydrogen, said G being represented by G_1H, and said intermediates being represented by formula (III-a), can also be prepared by reacting an intermediate of formula (XXVII) with thionylchloride in a reaction-inert solvent, e.g. methylene chloride.



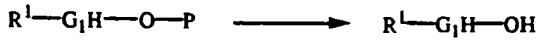
(XXVII) (III-a)

Intermediates of formula (XXVII) can be prepared by reducing an intermediate of formula (XXVIII) in a reaction-inert solvent, e.g. an alcohol, in the presence of a suitable reducing agent, e.g. sodium borohydride.



(XXVIII) (XXVII)

Alternatively, intermediates of formula (XXVII) can also be prepared by deprotecting an intermediate of formula (XXIX), wherein P is a suitable protecting group, e.g. C_{1-4}alkylcarbonyl, in a reaction-inert solvent, such as an alcohol, in the presence of a suitable base, e.g. sodium hydroxide.

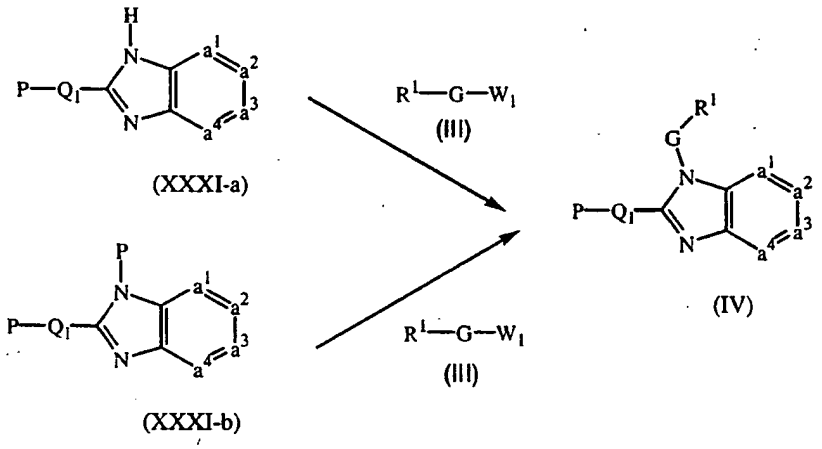


(XXIX) (XXVII)

Intermediates of formula (XXVIII), wherein $G_1(=O)$ is CH(=O), said intermediates being represented by formula (XXVIII-a), can be prepared by reacting an intermediate of formula (XXX), wherein W_3 is a suitable leaving group, such as a halo atom, e.g. bromo, with *N,N*-dimethylformamide in the presence of butyllithium in a reaction-inert solvent, e.g. tetrahydrofuran, diethylether or a mixture thereof.

(XXX) (XXVIII-a)

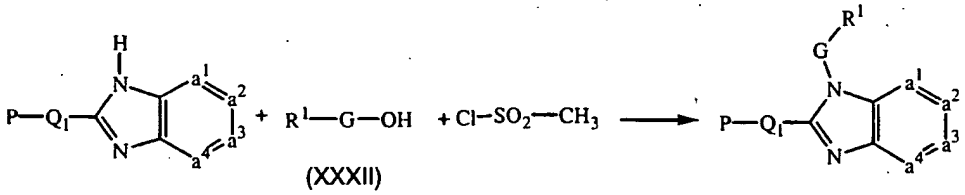
Intermediates of formula (IV) can be prepared by reacting an intermediate of formula (XXXI-a) or (XXXI-b), wherein P represents a suitable protecting group, such as, for example, C_{1-4}alkyloxycarbonyl, with an intermediate of formula (III) according to the reaction described for the general preparation of compounds of formula (I').



(XXXI-a) (III) (IV)

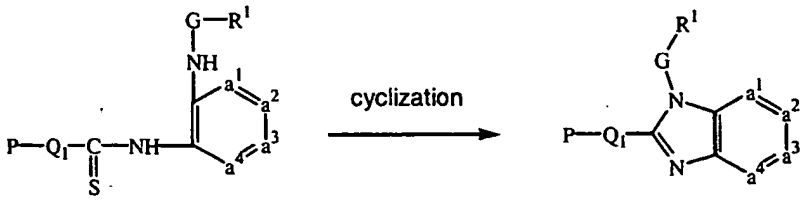
(XXXI-b) (III)

Intermediates of formula (IV) can also be prepared by reacting an intermediate of formula (XXXI-a) with an intermediate of formula (XXXII) that has reacted with methanesulfonyl chloride, in the presence of a suitable base, such as sodium hydride, and in the presence of a suitable reaction-inert solvent, e.g. *N,N*-dimethylformamide.



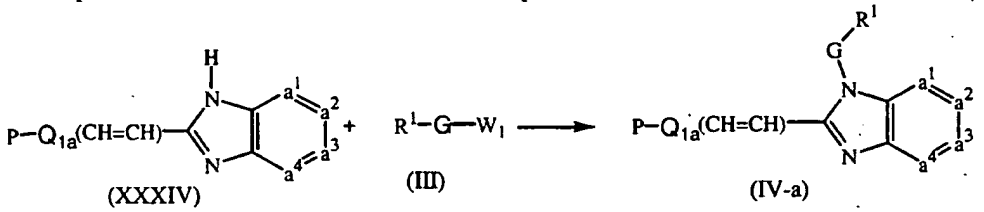
(XXXI-a) (XXXII) (IV)

Intermediates of formula (IV) can also be prepared by a cyclization reaction of an intermediate of formula (XXXIII) in a reaction-inert solvent, e.g. an alcohol or *N,N*-dimethylformamide, in the presence of mercury oxide and sulphur.



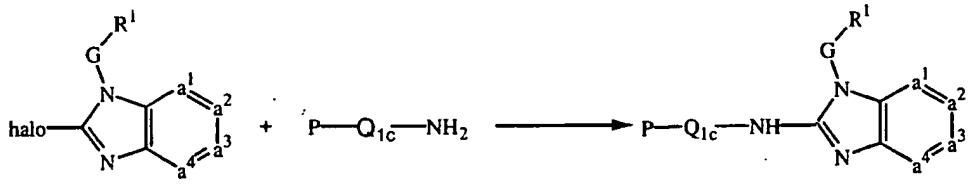
(XXXIII) (IV)

Intermediates of formula (IV) wherein Q_1 comprises an unsaturated bond, said Q_1 being represented by Q_{1a}(CH=CH), and said intermediates by formula (IV-a), can be prepared by reacting an intermediate of formula (XXXIV) with an intermediate of formula (III) in the presence of a suitable base, such as dipotassium carbonate.



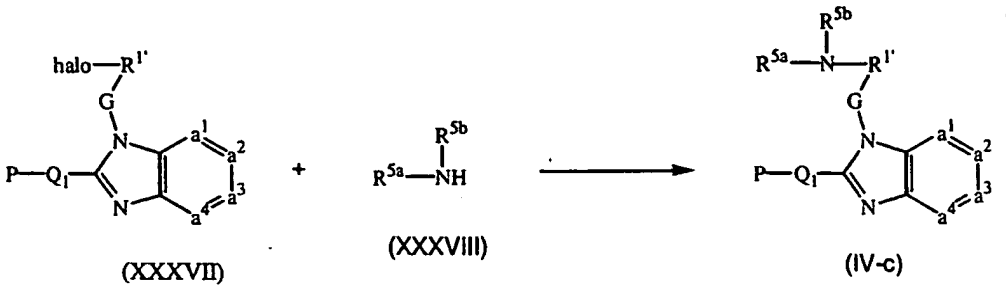
(XXXIV) (III) (IV-a)

Intermediates of formula (IV) wherein, in the definition of Q_1, the X^1 or X^2 moieties in the radicals of formula (b-1) to (b-8) represent NH, said Q_1 being represented by Q_{1c}-NH, and said intermediates by formula (IV-b), may also be prepared by reacting an intermediate of formula (XXXV) with an intermediate of formula (XXXVI).



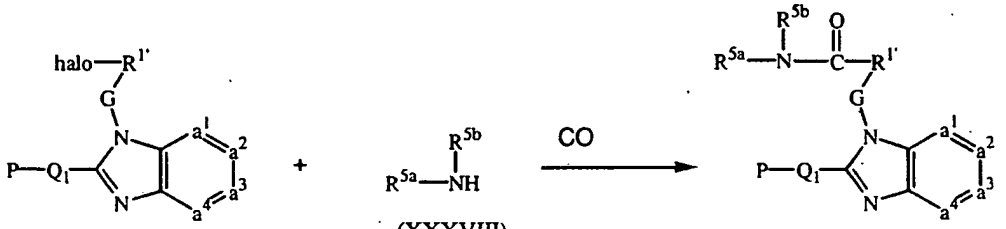
(XXXV) (XXXVI) (IV-b)

Intermediates of formula (IV) wherein R^1 is monocyclic heterocycle substituted with amino or mono- or di(C_{1-6}alkyl)amino, said R^1 being represented by $R^{5a}R^{5b}N$-$R^{1'}$, wherein R^{5a} and R^{5b} are defined as described hereinabove, and said intermediates being represented by formula (IV-c), can be prepared by reacting an intermediate of formula (XXXVII) with an appropriate amine, represented by formula (XXXVIII), in the presence of an appropriate catalyst, e.g. palladium, and (R)-(+)-2,2'-bis(diphenyl-phosphino)-1,1'-binaphtyl, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



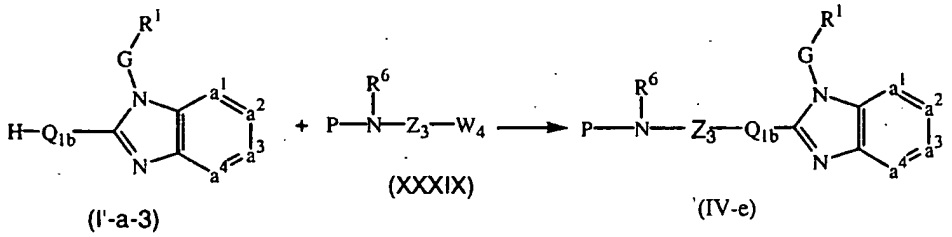
(XXXVII) (XXXVIII) (IV-c)

Intermediates of formula (IV) wherein R^1 is monocyclic heterocycle substituted with C(=O)-$NR^{5a}R^{5b}$, wherein R^{5a} and R^{5b} are defined as described hereinabove, said R^1 being represented by $R^{5a}R^{5b}N$-C(=O)-$R^{1'}$, and said intermediates being represented by formula (IV-d), can be prepared by reacting an intermediate of formula (XXXVII) with an appropriate amine, represented by formula (XXXVIII), under an atmosphere of carbon monoxide, in the presence of a suitable catalyst, e.g. palladium (II) acetate, and 1,3-bis(diphenylphosphino)propane, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



(XXXVII) (XXXVIII) (IV-d)

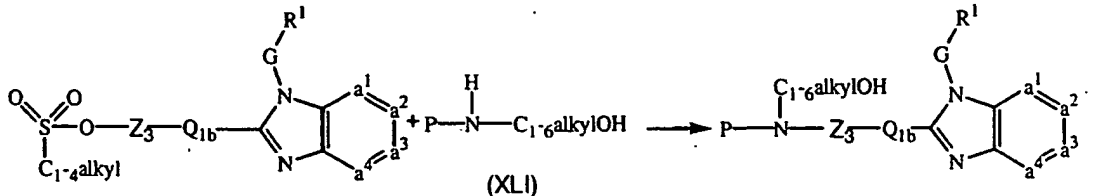
Intermediates of formula (IV) wherein P-Q_1 comprises C_{1-10}alkyl or C_{3-7}cycloalkyl substituted with NR^6-P, said C_{1-10}alkyl or C_{3-7}cycloalkyl being represented by Z_3, said P-Q_1 being represented by P-N R^6-Z_3-Q_{1b}, and said intermediates being represented by formula (IV-e), can be prepared by reacting a compound of formula (I'-a-3) with an intermediate of formula (XXXIX), wherein W_4 represents a suitable leaving group, such as p-toluenesulphonate. Said reaction can be performed in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



(I'-a-3) (XXXIX) (IV-e)

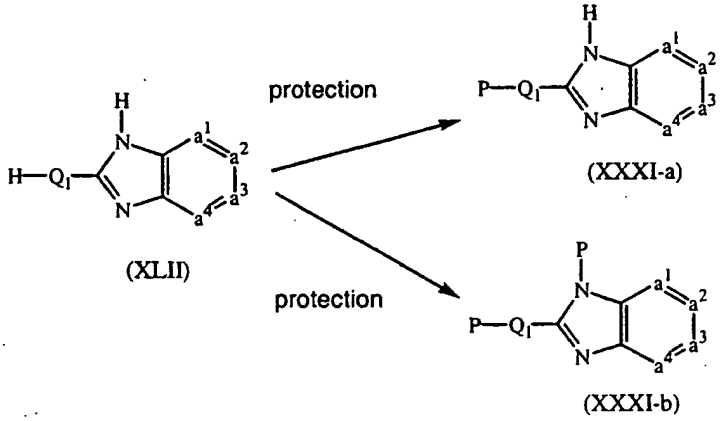
Intermediates of formula (IV-e), wherein R^6 is hydroxyC_{1-6}alkyl, said intermediates being represented by formula (IV-e-1), can be prepared by reacting an intermediate of

formula (XL) with an intermediate of formula (XLI) in the presence of a suitable base, e.g. dipotassium carbonate, and a suitable solvent, e.g. acetonitrile.



(XL) (XLI) (IV-e-1)

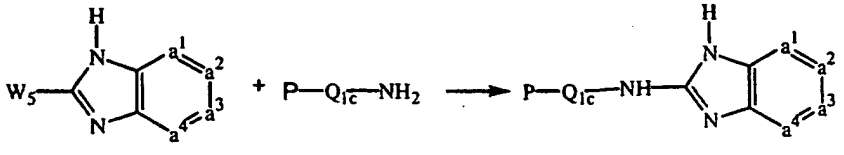
Intermediates of formula (XXXI-a) or (XXXI-b) can be prepared by protecting an intermediate of formula (XLII) with a suitable protecting group, such as, for example, C_{1-4}alkyloxycarbonyl, in a reaction-inert solvent, such as methylene chloride or an alcohol, e.g. methanol, ethanol, 2-propanol and the like, in the presence of a suitable reagent, e.g. diC_{1-4}alkyldicarbonate, and optionally in the presence of a suitable base, e.g. sodium acetate.



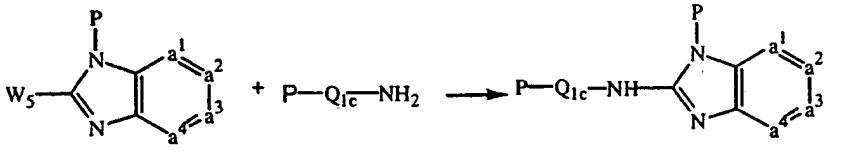
(XLII) (XXXI-a) (XXXI-b)

Alternatively, intermediates of formula (XXXI-a) or (XXXI-b) can be converted into an intermediate of formula (XLII) by reaction with a suitable acid, such as hydrochloric acid or hydrobromic acid and the like or mixtures thereof, in the presence of a suitable solvent, e.g. water.

Intermediates of formula (XXXI-a) or (XXXI-b), wherein in the definition of Q_1, the X^1 or X^2 moieties in the radicals of formula (b-1) to (b-8) represent NH, said Q_1 being represented by Q_{1c}-NH, and said intermediates by formula (XXXI-a-1) or (XXXI-b-1), can be prepared by reacting an intermediate of formula (XLIII-a) or (XLIII-b), wherein W_5 represents a suitable leaving group, such as for example a halo atom, e.g. chloro, with an intermediate of formula (XLIV).

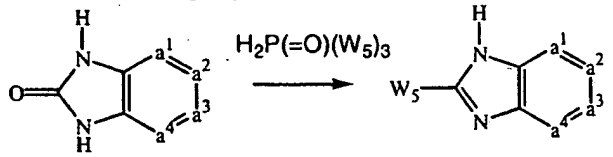


(XLIII-a) (XLIV) (XXXI-a-1)

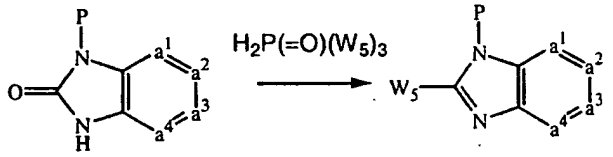


(XLIII-b) (XLIV) (XXXI-b-1)

Intermediates of formula (XLIII-a) or (XLIII-b) can be prepared by reacting an intermediate of formula (XLV-a) or (XLV-b) with $H_2P(=O)(W_5)_3$ in the presence of a suitable acid, e.g. hydrochloric acid.

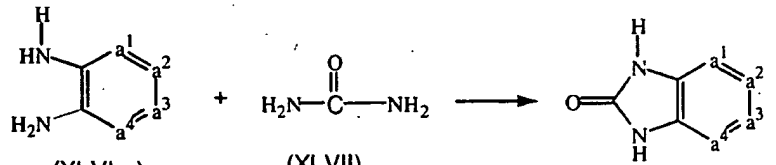


(XLV-a) (XLIII-a)

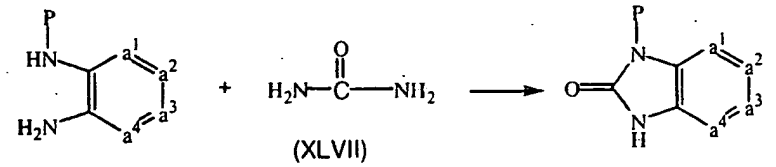


(XLV-b) (XLIII-b)

Intermediates of formula (XLV-a) or (XLV-b) can be prepared by reacting an intermediate of formula (XLVI-a) or (XLVI-b) with an intermediate of formula (XLVII).

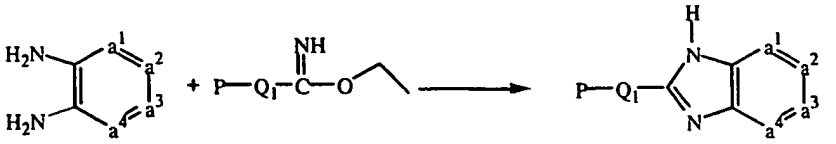


(XLVI-a) (XLVII) (XLV-a)



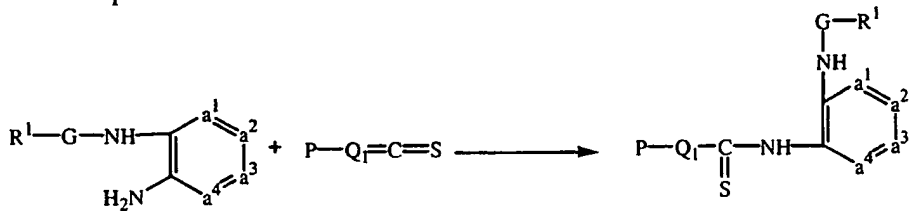
(XLVI-b) (XLVII) (XLV-b)

Intermediates of formula (XXXI-a) can also be prepared by reacting an intermediate of formula (XLVI-a) with $P\text{-}Q_1\text{-}C(=NH)\text{-}O\text{-}CH_2\text{-}CH_3$ in a reaction-inert solvent, such as an alcohol.



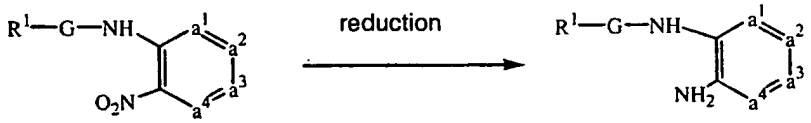
(XLVI-a) (XXXI-a)

Intermediates of formula (XXXIII) can be prepared by reacting an intermediate of formula (XLVIII) with an intermediate of formula $P\text{-}Q_1\text{=}C\text{=}S$, which is synthesized according to the procedures described in EP 0005318, in a reaction-inert solvent, such as an alcohol, e.g. ethanol. To increase the reaction rate, the reaction may be performed at elevated temperatures.



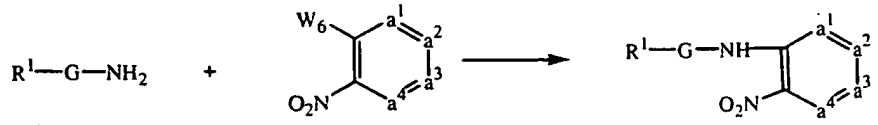
(XLVIII) (XXXIII)

Intermediates of formula (XLVIII) can be obtained by reducing an intermediate of formula (IL) in a reaction-inert solvent, e.g. an alcohol, in the presence of a suitable reducing agent, e.g. hydrogen, and an appropriate catalyst, e.g. Raney Nickel.



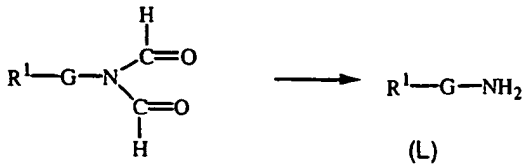
(IL) (XLVIII)

Intermediates of formula (IL) can be prepared by reacting an intermediate of formula (L) with an intermediate of formula (LI), in which W_6 represents a suitable leaving group, such as a halo atom, e.g. chloro. The reaction may be performed in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



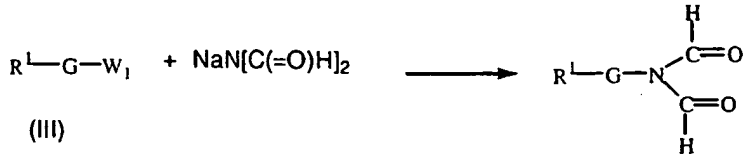
(L) (LI) (IL)

Intermediates of formula (L) can be prepared by reacting an intermediate of formula (LII) with a suitable acid, such as hydrochloric acid, in the presence of a suitable solvent, e.g. an alcohol, e.g. ethanol.



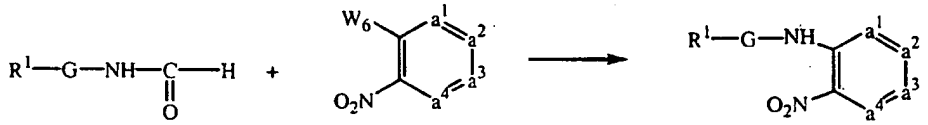
(LII) (L)

Intermediates of formula (LII) can be prepared by reacting an intermediate of formula (III) with $NaN[C(=O)H]_2$.



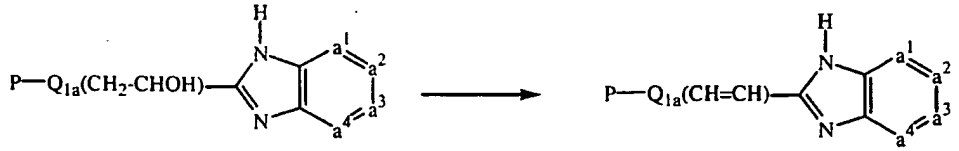
(III) (LII)

Intermediates of formula (IL) can also be prepared by reacting an intermediate of formula (LI) with an intermediate of formula (LIII) (J. Org. Chem., 25, p 1138, 1960) in a reaction-inert solvent, e.g. *N,N*-dimethylformamide, in the presence of an appropriate base, e.g. sodium hydride.



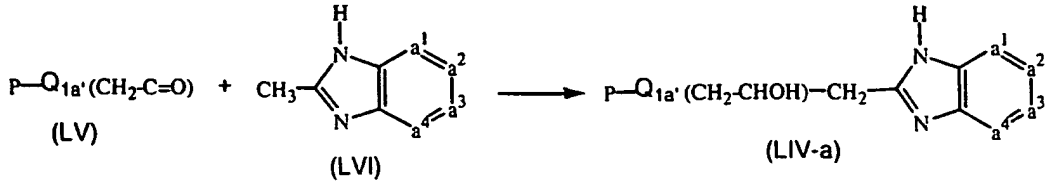
(LIII) (LI) (IL)

Intermediates of formula (XXXIV) can be prepared by dehydrating an intermediate of formula (LIV) with a suitable acid, such as sulfuric acid.



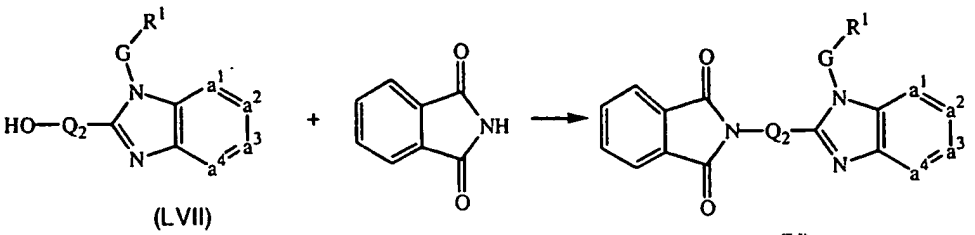
(LIV) (XXXIV)

Intermediates of formula (LIV) wherein, in the definition of Q_{1a}, the X^1 or X^2 moieties are CH_2, said Q_{1a} being represented by $Q_{1a'}$, and said intermediates being represented by formula (LIV-a), can be prepared by reacting a carbonyl moiety of formula (LV) with an intermediate of formula (LVI) in the presence of *N,N*-diisopropylamine and butyl lithium, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



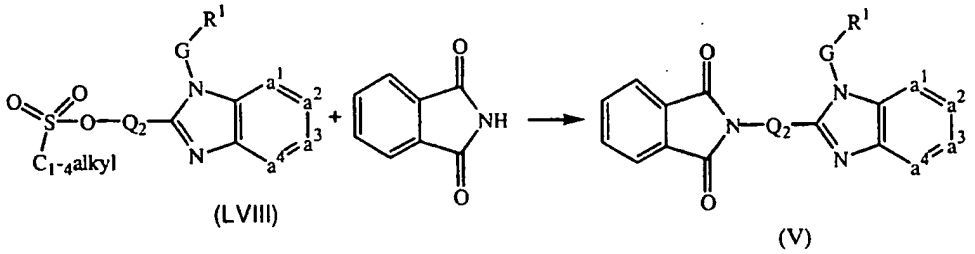
(LV) (LVI) (LIV-a)

Intermediates of formula (V) can be prepared by reacting an intermediate of formula (LVII) with 1*H*-isoindole-1,3 (2*H*)-dione in the presence of triphenylphosphine and diethyl azodicarboxylate.



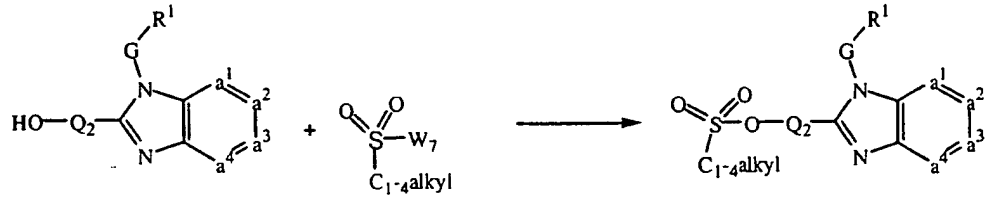
(LVII) (V)

Intermediates of formula (V) may also be prepared by reacting an intermediate of formula (LVIII) with 1*H*-isoindole-1,3 (2*H*)-dione in the presence of a suitable base, such as sodium hydride, and a suitable solvent, such as *N*, *N* -dimethylformamide.



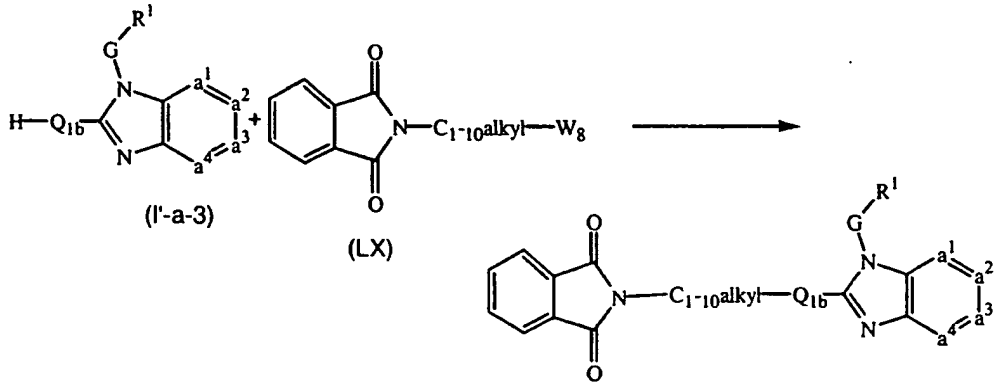
(LVIII) (V)

Intermediates of formula (LVIII) can be prepared by reacting an intermediate of formula (LVII) with an intermediate of formula (LIX), wherein W_7 represents a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, such as *N*, *N* -diethyl-ethanamine, and a suitable solvent, such as methylene chloride.



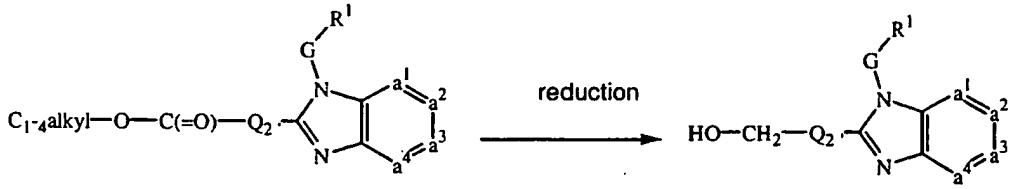
(LVII) (LIX) (LVIII)

Intermediates of formula (V), wherein in the definition of Q_2, R^2 is C_{1-10}alkyl, said Q_2 being represented by C_{1-10}alkyl-Q_{1b}, and said intermediates by formula (V-a), can be prepared by reacting a compound of formula (I'-a-3) with an intermediate of formula (LX), wherein W_8 is a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, such as dipotassium carbonate, and a suitable solvent, such as acetonitrile.



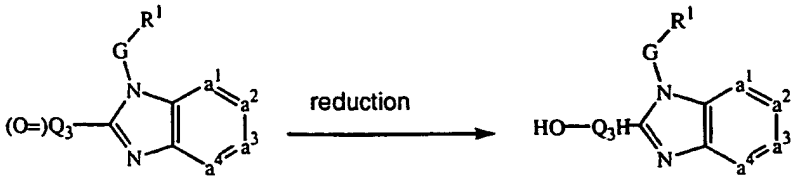
(I'-a-3) (LX) (V-a)

Intermediates of formula (LVII) wherein, in the definition of Q_2, the carbon atom carrying the hydroxy, also carries two hydrogen atoms, said HO-Q_2 being represented by HO-CH_2-Q_2', and said intermediates being represented by formula (LVII-a), can be prepared by reducing an intermediate of formula (LXI) in the presence of a suitable reducing agent, such as lithium aluminium hydride, in a suitable reaction-inert solvent, e.g. tetrahydrofuran.



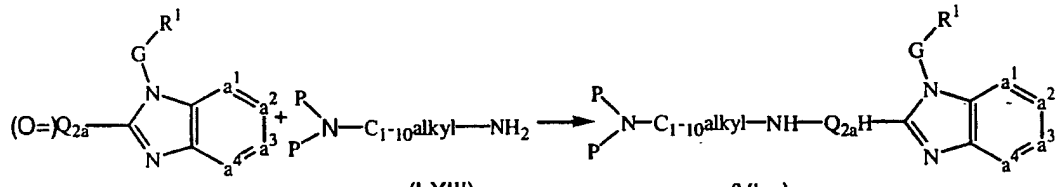
(LXI) (LVII-a)

Intermediates of formula (LVII), wherein, in the definition of Q_2, the carbon atom carrying the hydroxy, carries also at least one hydrogen, said HO-Q_2 being represented by HO-Q_3H, and said intermediates being represented by formula (LVII-b), can be prepared by reducing an intermediate of formula (IX) with a suitable reducing agent, e.g. sodium borohydride, in a reaction-inert solvent, e.g. an alcohol.



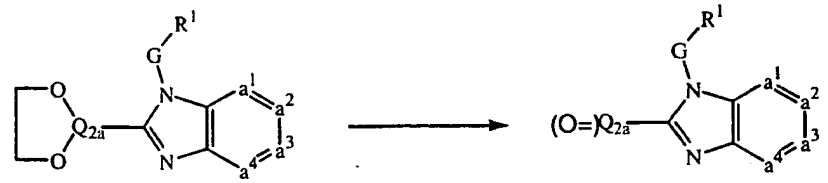
(IX) (LVII-b)

Intermediates of formula (VI) wherein, in the definition of Q_2, R^2 is C_{1-10}alkyl substituted with $N(P)_2$ and the carbon atom adjacent to the nitrogen atom carrying the R^2 substituent carries also at least one hydrogen atom, said Q_2 being represented by $(P)_2$-N-C_{1-10}alkyl-NH-$Q_{2a}H$, and said intermediates being represented by formula (VI-a), can be prepared by reductive amination of an intermediate of formula (LXII) with an intermediate of formula (LXIII) in the presence of a suitable reductive agent, such as hydrogen, and a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal, and the like, and optionally in the presence of a suitable catalyst poison, such as a thiophene solution. A suitable solvent in this reaction is a reaction-inert solvent, such as an alcohol.



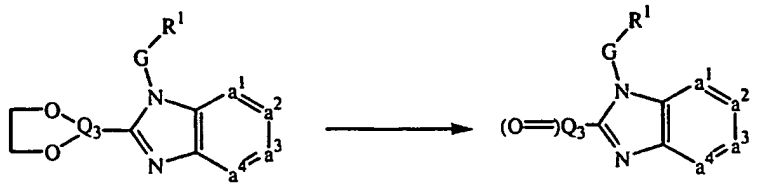
(LXII) (LXIII) (VI-a)

Intermediates of formula (LXII) can be prepared by deprotecting an intermediate of formula (LXIV) in the presence of a suitable acid, such as hydrochloric acid and the like, in a suitable solvent, e.g. water.



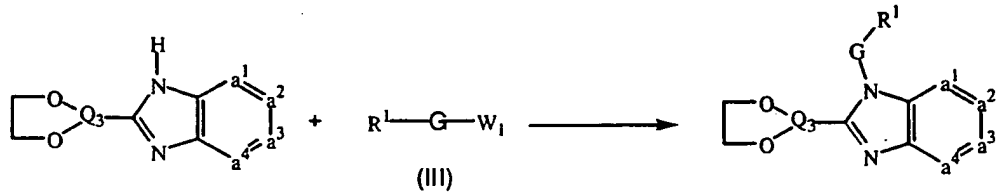
(LXIV) (LXII)

Intermediates of formula (IX) may be prepared by deprotecting an intermediate of formula (LXV) in the presence of a suitable acid, e.g. hydrochloric acid and the like.



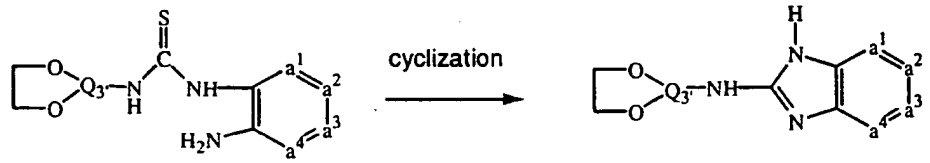
(LXV) (IX)

Intermediates of formula (LXV) can be prepared by reacting an intermediate of formula (LXVI) with an intermediate of formula (III) in the presence of a suitable base, e.g. dipotassium carbonate, in a suitable reaction-inert solvent, e.g. acetonitrile.



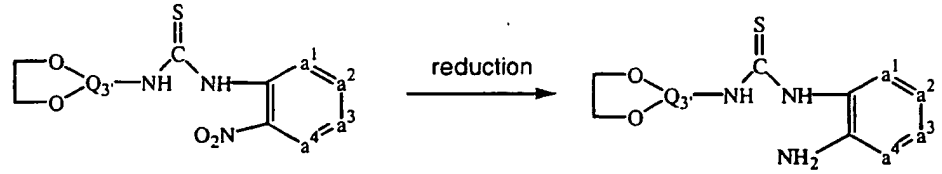
(LXVI) (III) (LXV)

Intermediates of formula (LXVI) wherein, in the definition of Q_3, the X^1 or X^2 moiety of the radicals of formula (b-1) to (b-8) represent NH, said Q_3 being represented by $Q_{3'}$-NH, and said intermediates being represented by formula (LXVI-a), may be prepared by cyclizing an intermediate of formula (LXVII) in the presence of mercury oxide and sulphur, in a suitable reaction-inert solvent, e.g. an alcohol.



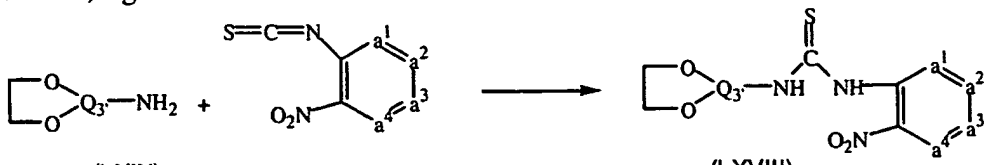
(LXVII) (LXVI-a)

Intermediates of formula (LXVII) can be prepared by reducing an intermediate of formula (LXVIII) in the presence of a suitable reducing agent, such as hydrogen, in the presence of a suitable catalyst, such as palladium-on-charcoal, platinum-on-charcoal and the like, in a suitable solvent, e.g. a mixture of ammonia in alcohol. Suitable alcohols are methanol, ethanol, 2-propanol and the like.



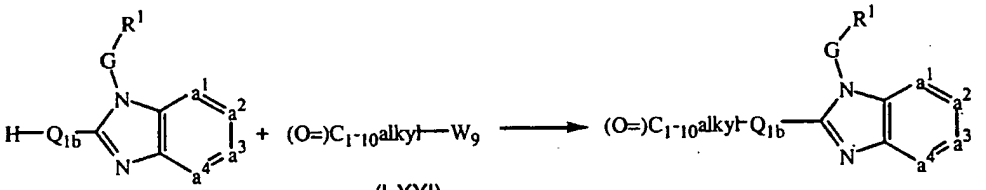
(LXVIII) (LXVII)

Intermediates of formula (LXVIII) can be prepared by reacting an intermediate of formula (LXIX) with an intermediate of formula (LXX) in a suitable reaction-inert solvent, e.g. ethanol.



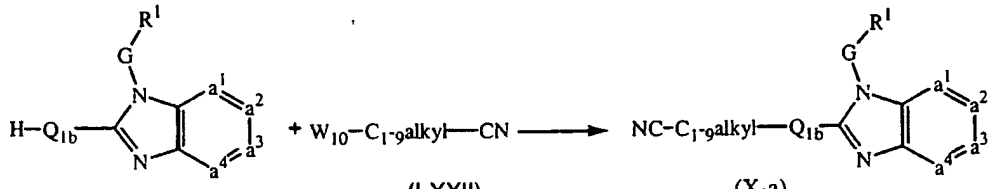
(LXIX) (LXX) (LXVIII)

Intermediates of formula (IX), wherein, in the definition of Q_3, R^2 comprises C_{1-10}alkyl, said Q_3 being represented by C_{1-10}alkyl-Q_{1b}, and said intermediates being represented by formula (IX-a), can be prepared by reacting a compound of formula (I'-a-3) with a reagent of formula (LXXI), wherein (O=)C_{1-10}alkyl represents a carbonyl derivative of C_{1-10}alkyl and wherein W_9 is a suitable leaving group, such as a halo atom, e.g. bromo, in a reaction-inert solvent, e.g. acetonitrile, in the presence of a suitable base, e.g. dipotassium carbonate.



(I'-a-3) (LXXI) (IX-a)

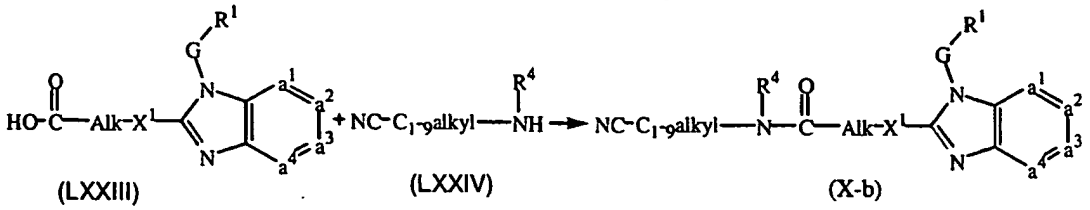
Intermediates of formula (X) wherein Q_4 comprises C_{1-9}alkyl, said Q_4 being represented by C_{1-9}alkyl-Q_{1b}, and said intermediates being represented by formula (X-a), can be prepared by reacting a compound of formula (I'-a-3) with a reagent of formula (LXXII), wherein W_{10} represents a suitable leaving group, such as a halo atom, e.g. chloro, in a reaction-inert solvent, e.g. 3-methyl-2-butanone, in the presence of a suitable base, e.g. dipotassium carbonate, sodium bicarbonate and the like.



(I'-a-3) (LXXII) (X-a)

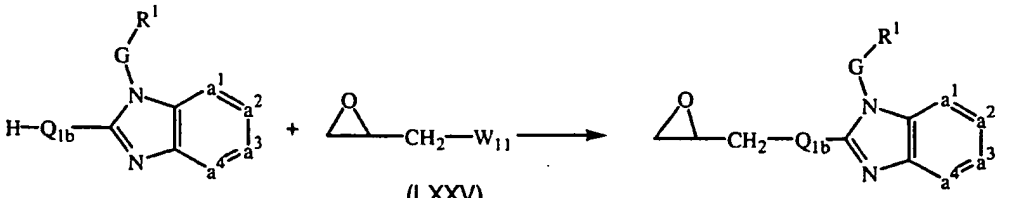
Intermediates of formula (X), wherein NC-Q_4 represents NC-(C_{1-9}alkyl)(R^4)N-C(=O)-Alk-X^1, said intermediates being represented by formula (X-b), can be prepared by reacting an intermediate of formula (LXXIII) with an intermediate of formula (LXXIV)

in the presence of di-1*H*-imidazol-2-yl-methanone, a suitable base, such as *N*, *N* -diethyl-ethanamine, and a suitable solvent, such as methylene chloride.



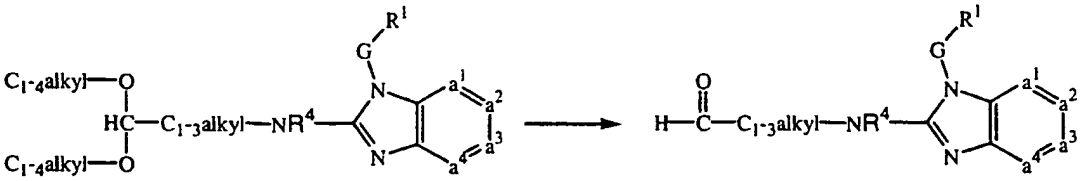
(LXXIII) (LXXIV) (X-b)

Intermediates of formula (XI), wherein Q_4 represents Q_{1b}, said intermediates being represented by formula (XI-a), can be prepared by reacting a compound of formula (I'-a-3) with an intermediate of formula (LXXV), wherein W_{11} represents a suitable leaving group, such as a halo atom, e.g. chloro, in the presence of a suitable base, such as disodium carbonate, and in the presence of a suitable solvent, such as 3-methyl-2-butanone.



(I'-a-3) (LXXV) (XI-a)

Intermediates of formula (XIX) can be prepared by reacting an intermediate of formula (LXXVI) with a suitable acid, such as hydrochloric acid.



(LXXVI) (XIX)

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g., counter-current distribution, liquid chromatography and the like.

The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid, respectively chiral base.

Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I), (I') or the compounds of group (I'') or any subgroup thereof, show antiviral properties. Viral infections treatable using the compounds and methods of the present invention include those infections brought on by ortho- and paramyxoviruses and in particular by human and bovine respiratory syncytial virus (RSV).

The *in vitro* antiviral activity against RSV of the present compounds was tested in a test as described in the experimental part of the description, and may also be demonstrated in a virus yield reduction assay. The *in vivo* antiviral activity against RSV of the present compounds may be demonstrated in a test model using cotton rats as described in Wyde et al. (Antiviral Research (1998), 38, 31-42).

Due to their antiviral properties, particularly their anti-RSV properties, the compounds of formula (I), (I') or the compounds of group (I'') or any subgroup thereof, their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms, are useful in the treatment of individuals experiencing a viral infection, particularly a RSV infection, and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses, in particular the respiratory syncytial virus.

The compounds of formula (I') or the compounds of group (I'') or any subgroup thereof may therefore be used as medicines. In particular, the compounds of formula (I), (I') or the compounds of group (I'') may be used in the manufacture of a medicament for the treatment or the prevention of viral infections, especially RSV infections. The use as a medicine or method of treatment comprises the systemic administration to viral infected

subjects or to subjects susceptible to viral infections of an amount effective to combat the conditions associated with the viral infection, in particular the RSV infection.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form or as metal complex, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

The compounds of the present invention may also be administered via oral inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry powder, a solution being preferred. Any system developed for the delivery of solutions,

suspensions or dry powders via oral inhalation or insufflation are suitable for the administration of the present compounds.

Thus, the present invention also provides a pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising a compound of formula (I') or a compound of the group (I'') and a pharmaceutically acceptable carrier. Preferably, the compounds of the present invention are administered via inhalation of a solution in nebulized or aerosolized doses.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, suppositories, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

In general it is contemplated that an antivirally effective daily amount would be from 0.01 mg/kg to 500 mg/kg body weight, more preferably from 0.1 mg/kg to 50 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

It may be appropriate to administer an antivirally effective daily dosage as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms.

The exact dosage and frequency of administration depends on the particular compound of formula (I), (I') or a compound of group (I'') used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

Also, the combination of another antiviral agent and a compound of formula (I), (I') or a compound of the group (I'') can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I), (I') or a compound of the group (I''), and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in antiviral treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. For instance, the compounds of the present invention may be combined with interferon-beta or tumor necrosis factor-alpha in order to treat or prevent RSV infections.

The following examples are intended to illustrate the present invention.

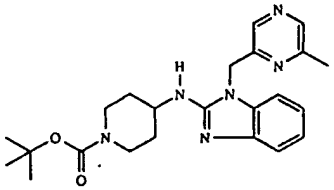
Experimental part

Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "DIPE" is defined as diisopropylether, "DMSO" is defined as dimethylsulfoxide, and "THF" is defined as tetrahydrofuran.

Preparation of the intermediate compounds

Example A1

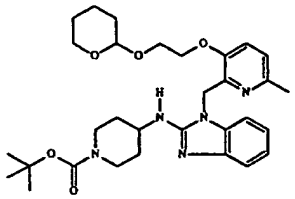
a) $NaOCH_3$ (0.2 mol) was added to a mixture of *N*-(4-piperidinyl)-1*H*-benzimidazol-2-amine dihydrobromide (0.1 mol) in methanol (389ml), the mixture was cooled on an ice bath and stirred for 2 hours. Bis(1,1-dimethylethyl) dicarbonoate (0.1mol) was added to a cooled mixture on an ice bath and then stirred for 18 hours at room temperature. The mixture was evaporated and suspended in water/DIPE. The residue was filtered off, washed with water/DIPE and dried. The residue was boiled up in CH_3OH. Yield : 17.46g of 1,1-dimethylethyl 4-(1*H*-benzimidazol-2-ylamino)-1-piperidinecarboxylate (55.2%) (interm. 1).

b) Preparation of  (interm. 2)

1-Bromo-2,5-pyrrolidinedione (0.055 mol) and then dibenzoyl peroxide (cat.quant.) were added to a mixture of 2,6-dimethylpyrazine (0.05 mol) in CCl_4 (100ml). The mixture was stirred and refluxed for 4 hours, stirred at room temperature under N_2 flow overnight, cooled on an ice bath and filtered. The filtrate was evaporated, to give residue 1. NaH (0.04 mol) was added to a solution of intermediate (1) (0.04 mol) in DMF (150ml). The mixture was stirred at room temperature under N_2 flow for 1 hour. Residue 1 was dissolved in DMF (50ml) and added dropwise to the mixture. The mixture was stirred at 50°C overnight. DMF was evaporated. The residue was taken

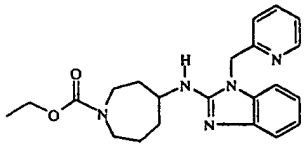
up in H_2O and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated. Yield: 6.82g of intermediate (2) (32%).

Example A2

Preparation of  (interm. 3)

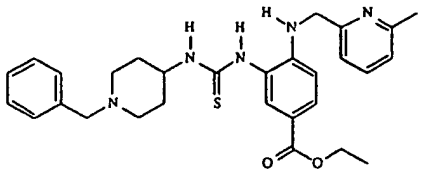
Reaction under N_2 flow. NaH 60% (0.02 mol) was added to a mixture of (±)-6-methyl-3-[2-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethoxy]-2-pyridinemethanol (0.02 mol) in DMF (75ml). Methanesulfonyl chloride (0.02 mol) was added. The mixture was added at room temperature to a mixture of intermediate (1) (0.02 mol) and NaH (0.022 mol) in DMF (100ml), previously stirred at 40°C for 1 hour. The mixture was stirred at room temperature overnight. The solvent was evaporated. The residue was taken up in H_2O and CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ (CH_3OH/NH_3) 97/3). The pure fractions were collected and the solvent was evaporated. Yield: 3.52g of intermediate (3) (31%).

Example A3

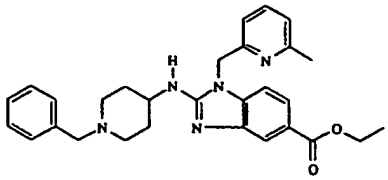
Preparation of  (interm. 4)

2-Chloro-1-(2-pyridylmethyl)-1*H*-benzimidazole (0.0615 mol) and ethyl 4-amino-hexahydro-1*H*-azepine-1-carboxylate (0.123 mol) were stirred at 160°C for 3 hours. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (13.6g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98/2/0.1). The pure fractions were collected and the solvent was evaporated. Yield: 10.5g of intermediate (4) (43%).

Example A4

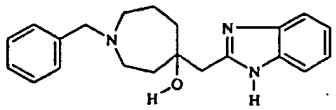
a) Preparation of  (interm. 5)

A mixture of ethyl 3-amino-4-[[(6-methyl-2-pyridyl)methyl]amino]benzoate (0.166 mol) and 4-isothiocyanato-1-(phenylmethyl)piperidine (0.166 mol) in ethanol (500ml) was stirred and refluxed for 8 hours and at room temperature overnight. The precipitate was filtered off and used without further purification. Yield: intermediate (5).

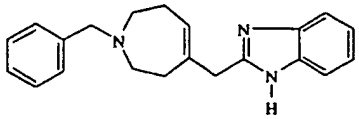
b) Preparation of  (interm. 6)

A mixture of intermediate (5) (0.16 mol), HgO (0.192 mol) and S (spat.tip) in DMF (100ml) was stirred at 80°C for 4 hours, filtered warm over dicalite, washed with warm DMF, heated again and filtered warm over dicalite. The solvent was evaporated. The residue was taken up in CH_2Cl_2. The mixture was washed with H_2O. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was co-evaporated with toluene. The residue was crystallized from CH_3CN. The precipitate was filtered off and dried. Yield: 53.5g of intermediate (6) (70%)

Example A5

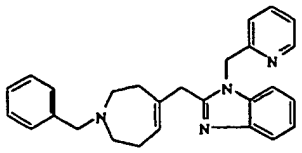
a) Preparation of  (interm. 7)

A mixture of *N*-(1-methylethyl)-2-propanamine (0.098 mol) in THF (100ml) was stirred at -40°C under N_2 flow. BuLi 1.6M in hexane (0.098 mol) was added dropwise. The mixture was stirred at -40°C for 30 min and cooled to -70°C. A mixture of 1-(diethoxymethyl)-2-methyl-1*H*-benzimidazole (0.098 mol) in THF (50ml) was added dropwise and the mixture was stirred for 45 minutes. A mixture of hexahydro-1-(phenylmethyl)-4*H*-azepin-4-one (0.049 mol) in THF (50ml) was added dropwise at -70°C. The mixture was hydrolized cold and extracted with EtOAc. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2). The pure fractions were collected and the solvent was evaporated (yielding 7.5g). Part of the residue (3.5g) was crystallized from EtOAc. The precipitate was filtered off and dried. Yield: 2.3g of intermediate (7).

b) Preparation of  (interm. 8)

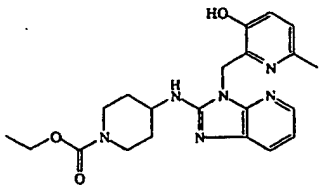
A mixture of intermediate (7) (0.029 mol) in 1,1'-oxybis[2-methoxyethane] (300ml) and H_2SO_4 conc. (20ml) was stirred at 160°C for 24 hours. Ice water was added. The mixture was basified with K_2CO_3 solid and extracted with CH_2Cl_2. The organic layer

was separated, dried, filtered and the solvent was evaporated. Yield: 18g of a mixture of 2 compounds, of which one compound is intermediate (8) (75%).

c) Preparation of  (interm. 9)

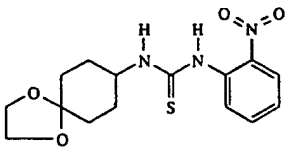
A mixture of intermediate (8), 2-(chloromethyl)pyridine (0.047 mol) and K_2CO_3 (0.0775 mol) in acetonitrile (500ml) was stirred and refluxed for 24 hours. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. Yield: 15.4g of a mixture of 2 compounds, of which one is intermediate (9).

Example A6

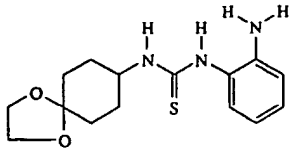
Preparation of  (interm. 10)

N,*N*-diethylethamine (16ml) and then 2-chloromethyl-6-methyl-3-pyridinol (0.0376 mol) were added to a mixture of ethyl 4-[(3*H*-imidazo[4,5-b]pyridin-2-yl)amino]-1-piperdinecarboxylate (0.0376 mol) in DMF (550ml). The mixture was stirred at room temperature for 3 hours and at 50°C overnight. The solvent was evaporated. The residue was poured out into H_2O and CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by HPLC over silica gel (eluent: CH_2Cl_2/C_2H_5OH 95/5 to 70/30). The desired fraction was collected and the solvent was evaporated. Yield: 2.1 g of intermediate (10).

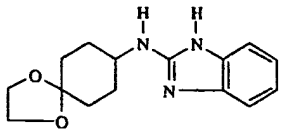
Example A7

a) Preparation of  (interm. 11)

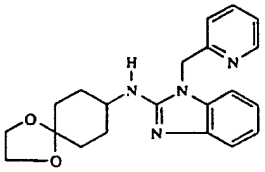
A mixture of 1,4-dioxaspiro[4,5]decan-8-amine (0.28 mol) and 1-isothiocyanato-2-nitrobenzene (0.28 mol) in ethanol (300ml) was stirred at room temperature for 2 hours. The solvent was evaporated. The product was used without further purification. Yield: 90g of intermediate (11).

b) Preparation of  (interm. 12)

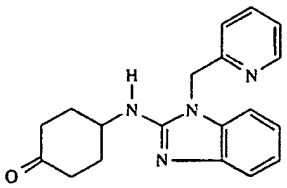
A mixture of intermediate (11) (0.178 mol) in NH_3/CH_3OH (500ml) and THF (100ml) was hydrogenated at room temperature under a 3 bar pressure for 24 hours with Pd/C (52g) as a catalyst. After uptake of H_2 (3 equiv), the catalyst was filtered through celite, washed with CH_3OH and the filtrate was evaporated. The product was used without further purification. Yield: 44g of intermediate (12).

c) Preparation of  (interm. 13)

A mixture of intermediate (12) (0.071 mol), HgO (0.142 mol) and S (0.56g) in ethanol (300ml) was stirred and refluxed for 4 hours, filtered over celite, washed with CH_2Cl_2 and the filtrate was evaporated. The reaction was carried out again using the same quantities. The residues were combined and then purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 94/6/0.5; 20-45 µm). The pure fractions were collected and the solvent was evaporated. Yield: 14.5g of intermediate (13) (43%); mp. >260°C.

d) Preparation of  (interm. 14)

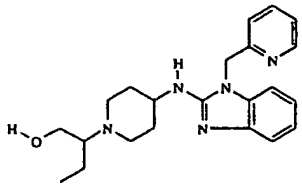
A mixture of intermediate (13) (0.049 mol), 2-(chloromethyl)pyridine (0.0735 mol) and K_2CO_3 (0.196 mol) in acetonitrile (325ml) was stirred and refluxed for 4 hours and then brought to room temperature. The reaction was carried out again using the same quantities. The mixtures were combined. H_2O was added and the mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 98/2/0.1; 20-45 µm). The pure fractions were collected and the solvent was evaporated. Part of this fraction (0.6g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.46g of intermediate (14); mp. 136°C.

e) Preparation of  (interm. 15)

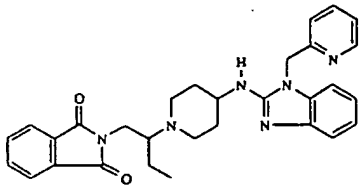
A mixture of intermediate (14) (0.077 mol) in HCl 3N (350ml) was stirred and refluxed for 1 hour, poured out into ice water, basified with K_2CO_3 solid and extracted with CH_2Cl_2. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered

and the solvent was evaporated. Part of the residue (1.5g) was crystallized from CH_3CN and diethyl ether. The precipitate was filtered off and dried. Yield: 0.5g of intermediate (15); mp. 148°C.

Example A8

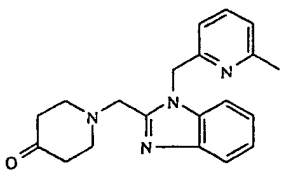
a) Preparation of  (interm. 16)

$LiAlH_4$ (0.023 mol) was added portionwise at 5°C to a solution of (±)-ethyl α-ethyl-4-[[1-(2-pyridylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidineacetate (0.021 mol) in THF (100ml). The mixture was stirred at 5°C for 1 hour. EtOAc was added. The mixture was hydrolized with ice water, filtered over celite, washed with EtOAc, dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 7.2g of intermediate (16) (88%).

b) Preparation of  (interm. 17)

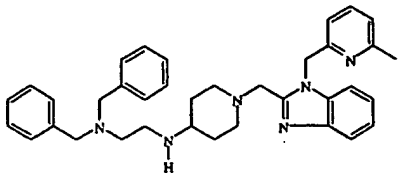
Diethyl azodicarboxylate (0.028 mol) was added slowly at room temperature to a solution of intermediate (16) (0.019 mol), 1*H*-isoindole-1,3(2*H*)-dione (0.028 mol) and triphenyl phosphine (0.028 mol) in THF (200ml). The mixture was stirred at room temperature for 8 hours. The solvent was evaporated till dryness. The residue was dissolved in CH_2Cl_2. The solution was acidified with HCl 3N, basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (12g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH/NH_4OH 97/3/0.1; 20-45 µm). The pure fractions were collected and the solvent was evaporated. Yield: 5.5g of intermediate (17) (57%).

Example A9

a) Preparation of  (interm. 18)

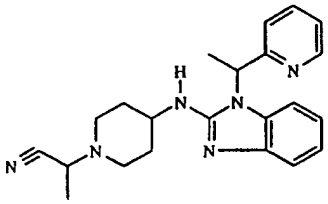
A mixture of 8-[[1-[(6-methyl-2-pyridyl)methyl]-1*H*-benzimidazol-2-yl]methyl]-1,4,8-dioxa-8-azaspiro[4.5]decane (0.0196 mol) in HCl 6N (55ml) and H_2O (55ml) was

stirred and refluxed for 6 hours. Toluene was added. The mixture was poured out on ice, alkalized with a NaOH solution and extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. Part of this fraction was suspended in DIPE, filtered off and dried. Yield: 0.32g of intermediate (18) (91%).

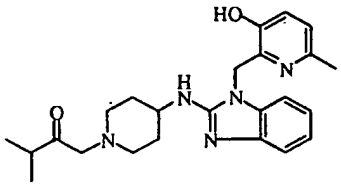
b) Preparation of  (interm. 19)

A mixture of intermediate (18) (0.008 mol) and *N,N*-dibenzylethylenediamine (0.01 mol) in methanol (150ml) was hydrogenated with Pd/C 10% (1g) as a catalyst in the presence of thiophene solution (0.5ml). After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. Yield: 5.39g of intermediate (19) (quant.).

Example A10

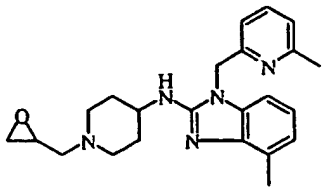
a) Preparation of  (interm. 20)

A mixture of (±)-*N*-(4-piperidinyl)-1-[1-(2-pyridyl)ethyl]-1*H*-benzimidazol-2-amine (0.026 mol), 2-chloropropanenitrile (0.039 mol) and K_2CO_3 (0.052 mol) in acetonitrile (100ml) was stirred and refluxed for 8 hours. H_2O was added and the mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (8.5g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 96/4; 20-45 µm). The pure fractions were collected and the solvent was evaporated. Yield: 4.5g of intermediate (20) (46%).

b) Preparation of  (interm. 22)

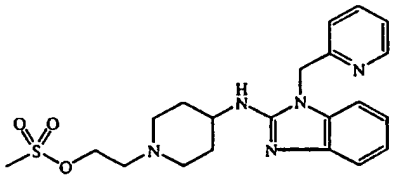
A mixture of compound 49 (0.0164 mol), 1-bromo-3-methyl-2-butanone (0.03 mol) and K_2CO_3 (0.06 mol) in CH_3CN (100ml) was stirred and refluxed for several hours. H_2O was added. The solvent was evaporated. 4-Methyl-2-pentanone was added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 98/2). The desired fractions were collected and the solvent was evaporated. Yield: 2.75g of intermediate (22) (40%).

Example A11

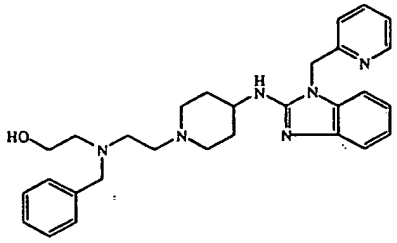
Preparation of  (interm. 21)

A mixture of compound 90 (0.015 mol), (chloromethyl)oxirane (0.008 mol) and Na_2CO_3 (1.59g) in 4-methyl-2-pentanone (150ml) was heated slowly to 100°C (to 40°C in 1 hour, 70°C in 1 hour), stirred at 100°C overnight, then stirred and refluxed for 20 hours. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 95/5). Two fractions were collected and their solvents were evaporated. Fraction 1 was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 0.18g of intermediate (21).

Example A12

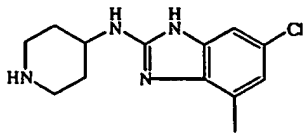
a) Preparation of  (interm. 23)

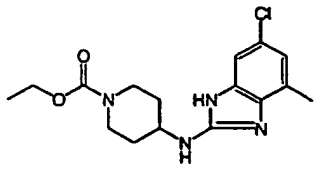
Methylsulfonyl chloride (0.0512 mol) was added dropwise at 0°C under N_2 flow to a mixture of 4-[[1-(2-pyridinylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidineethanol (0.0256 mol) and *N*,*N*-diethylethanamine (0.0512 mol) in CH_2Cl_2 (200ml). The mixture was stirred at room temperature for 90 minutes. The solvent was evaporated till dryness.. Yielding: intermediate (23)

b) Preparation of  (interm. 24)

A mixture of intermediate (23) (0.028 mol), 2-[(phenylmethyl)amino]ethanol, (0.034 mol) and K_2CO_3 (0.112 mol) in CH_3CN (200ml) was stirred at 60°C for 4 hours. H_2O was added and the mixture was extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (13.5g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/NH_4OH 97/3/0.5; 35-70 µm). The pure fractions were collected and the solvent was evaporated. Yield: 5.5g of intermediate (24) (41%).

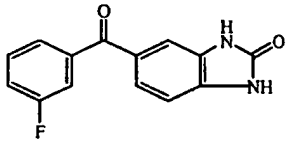
Example A13

Preparation of  (interm. 25)

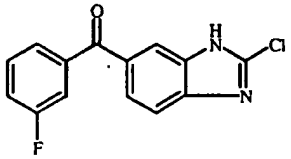
HCl 12N (165ml) was added to a mixture of  ,

(interm. 36), prepared according to example A7c), (0.049 mol) in H_2O (165ml). The mixture was stirred and refluxed for 6 hours. The solvent was evaporated. HBr 48% (320ml) was added. The mixture was stirred and refluxed for 4 hours and then stirred overnight. The solvent was evaporated. 2-Propanol was added and the solvent was evaporated again. The residue was suspended in DIPE. The mixture was decanted, taken up in H_2O/DIPE and then separated into its layers. CH_2Cl_2 was added to the aqueous layer. The mixture was alkalized with NH_4OH. 2-Propanol was added. The organic layer was separated, dried, filtered and the solvent was evaporated. Yield: 15g of intermediate (25).

Example A14

a) Preparation of  (interm. 26)

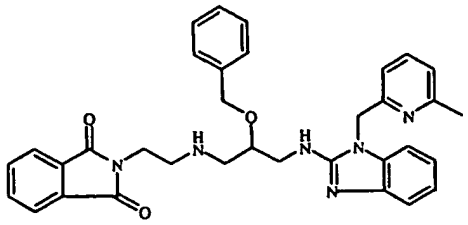
3,4-diaminophenyl-(3-fluorophenyl)methanone (0.056 mol) and urea (0.084 mol) were stirred at 150 à 160°C for 4 hours (melt) and then cooled. Water was added. The mixture was stirred at 50°C for a while and then cooled. The precipitate was filtered off, stirred in 2-propanone and dried. Yield: 11.4g of intermediate (26).

b) Preparation of  (interm. 27)

Phosphorus oxychloride (50ml) was added carefully to intermediate (26) (0.045 mol). The mixture was stirred and refluxed for 24 hours and then was stood at room temperature over the weekend. The solvent was evaporated. The residue was taken up in CH_2Cl_2/ice/K_2CO_3 solid. The mixture was separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The undissolved material was filtered off to give residue 1. The combined organic layer was dried, filtered and the solvent was evaporated to give residue 2. Residue 1 and residue 2 were combined. Yield: 16.75g

of intermediate (27) (100%).

Example A15

Preparation of  (interm. 28)

A mixture of compound (341) (0.0025 mol) , prepared according to B25a), 2-(2-bromoethyl)-1*H*-Isoindole-1,3(2*H*)-dione (0.00275 mol) and K_2CO_3 (3g) in CH_3CN (100ml) was stirred and refluxed for 24 hours. The solvent was evaporated. The residue was dissolved in CH_2Cl_2 and then washed with water. The organic layer was dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 97/3). The pure fractions were collected and the solvent was evaporated. Yield: intermediate (28).

Example A16

a) 2, 4,5-trimethyloxazole (0.225mol) was stirred in CCl_4 (500mL) under N_2-flow. Then 1-bromo-2,5-pyrrolidinedione (0.225mol) and benzoyl peroxide (cat.quant.) were added. This mixture was stirred and refluxed for 1hour under N_2-flow. The reaction mixture was cooled in an ice bath (ice/salt). The mixture was filtered. The filtrate was evaporated. Yield: 42.7g (<100%) of 5-(bromomethyl)-2,4-dimethyloxazole (intermediate 30).

b) Intermediate (30) (0.225 mol) was taken up in DMF (450ml). $Na[N(CH(=O))_2]$ (0.225 mol) was added portionwise and the mixture was stirred at 50°C for 1hour and at room temperature overnight. The mixture was evaporated. Yield : 41g (100%) of *N*-[(2,4-dimethyl-5-oxazolyl)methyl]-*N*-formylformamide (intermediate 31).

c) A mixture of intermediate (31) (0.225 mol) in HCl 36% (120ml) and ethanol (500ml) was refluxed for 1hour and stirred overnight. The mixture was filtered off, the precipitate was washed with C_2H_5OH and the filtrate was evaporated. The residue was taken up in ice water, alkalized with NaOH and extracted with CH_2Cl_2. The mixture was separated and the organic layer was dried and evaporated. Yield : 28g (100%) of 2,4-dimethyl-5-oxazolmethanamine (intermediate 32).

d) 2-chloro-3-nitropyridine (0.225 mol) and Na_2CO_3 (0.225 mol) were added to a mixture of intermediate (32) (0.225 mol) in ethanol (500ml) and the mixture was stirred and refluxed for 6hours. The mixture was evaporated and the residue was taken up in water and extracted with CH_2Cl_2. The mixture was separated and the organic layer was

dried, filtered off and evaporated. The residue was purified by column chromatography over silica gel. The pure fractions were collected and evaporated. Yield : 27g (48%) of *N*-[(2,4-dimethyl-5-oxazolyl)methyl]-3-nitro-2-pyridinamine (intermediate 33).

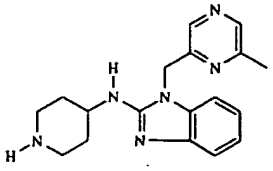
e) A mixture of intermediate (33) (0.1 mol) was hydrogenated in a thiophene solution 4% (3ml) and methanol (400ml) with Pd/C 5% (4g) as a catalyst. After uptake of H_2 (3eq), the catalyst was filtered off. The residue was evaporated and used without further purification. Yield : 21.8 g (100%) of N^2-[(2,4-dimethyl-5-oxazolyl)methyl]-2,3-pyridinediamine (intermediate 34).

f) Intermediate (34) (0.1 mol) was dissolved in DMF (250ml). Ethyl 4-isothiocyanato-1-piperidinecarboxylate (0.1 mol) was added and the mixture was stirred at 50°C for 20 hours. HgO (0.125 mol) and sulfur powder (few crystals) were added and the mixture was stirred at 75°C for 3hours 30minutes. The mixture was filtered over dicalite and the filtrate was evaporated. The residue was taken up in water/CH_2Cl_2. The mixture was separated, the organic layer was dried, filtered off and evaporated. The residue was purified by column chromatography over silica gel (eluent : CH_2Cl_2/CH_3OH 95/5). The pure fractions were collected and evaporated. The residue was crystallized from DIPE and recrystallized from CH_3CN. Yield : 216.6277g (55.4%) of ethyl 4-[[3-[(2,4-dimethyl-5-oxazolyl)methyl]-3*H*-imidazo[4,5-b]pyridin-2-yl]amino-1-piperidinecarboxylate (intermediate 35).

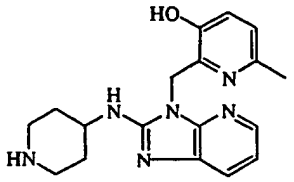
Example A17

Cl-CH_2-C(=NH)-O-C_2H_5 (0.0625 mol) was added to a mixture of N^2-[(2-methyl-5-oxazolyl)methyl]-2,3-pyridinediamine (0.05 mol) in acetic acid (150mL) and the mixture was stirred for 20 hours at room temperature. The mixture was warmed up to 90°C and stirred for 10 minutes at this temperature. The mixture was evaporated at <50°C. The residue was taken up in water/CH_2Cl_2 + Na_2CO_3. The organic layer was separated, extracted with CH_2Cl_2, dried ($MgSO_4$) and filtered. The residue was taken up in DIPE + active charcoal and stirred for 1hour. The mixture was filtered and evaporated, Yield : 13.1 g (100%) of 2-(chloromethyl)-3-[(2-methyl-5-oxazolyl)methyl]-3*H*-imidazo[4,5-b]pyridine (intermediate 29).Preparation of the final compounds

Example B1

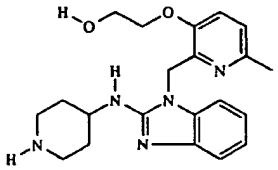
a) Preparation of  (compound 1)

A mixture of intermediate (2) (0.016 mol) in 2-propanol/HCl (10ml) and 2-propanol (100ml) was stirred and refluxed for 2 hours and then cooled. The precipitate was filtered off, washed with DIPE and dried. The residue was taken up in H_2O, NH_3 and CH_3OH and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/ (CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. Yield: 1.8g of compound (1) (35%).

b) Preparation of  (compound 308)

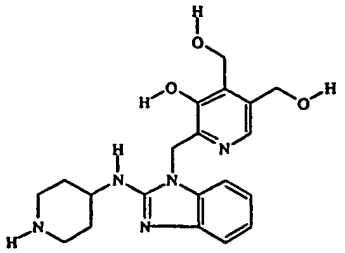
A mixture of intermediate (10) (0.0054 mol) in HBr 48% (50 ml) was stirred and refluxed for 5 hours. The solvent was evaporated. The residue was suspended in DIPE, filtered off and crystallized from ethanol. The solvent was evaporated and the fraction was purified by high-performance liquid chromatography over RP Hyperprep (eluent: (0.5% NH_4OAc in H_2O)/CH_3CN from 100/0 to 0/100). The pure fractions were collected and the solvent was evaporated. Yield: 0.188 g of compound (308).

Example B2

a) Preparation of  (compound 2)

HCl (1:3); H_2O (1:2)

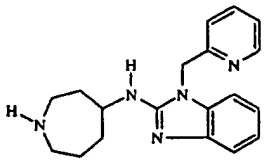
A mixture of intermediate (3) (0.00622 mol) in 2-propanol/HCl (10ml) and 2-propanol (100ml) was stirred and refluxed for 4 hours. The solvent was evaporated. The residue was taken up in H_2O, Na_2CO_3 and CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was dissolved in 2-propanol and DIPE and converted into the hydrochloric acid salt with 2-propanol/HCl. The precipitate was filtered off and dried. This fraction was converted into the free base and purified over silica gel on a glass filter (eluent: CH_2Cl_2/(CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was converted into the hydrochloric acid salt (1:3). The precipitate was filtered off and dried. Yield: 0.65g of compound (2) (20%).

b) Preparation of  (compound 3)

HCl (1:3); H_2O (1:2)

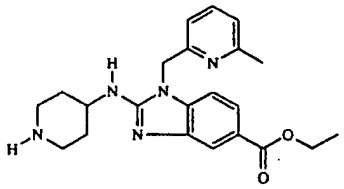
A mixture of 1,1-dimethylethyl 4-[[1-[[3,5-dihydro-3,3-dimethyl-9-(phenylmethoxy)-1*H*-[1,3]dioxepino[5,6-c]pyridin-2-yl]methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (0.00552 mol) in HCl 10N (200ml) was stirred and refluxed for 6 hours. The solvent was evaporated. The residue was suspended in DIPE, filtered off and dried. Yield: 0.58g of compound (3).

Example B3

Preparation of  (compound 4)

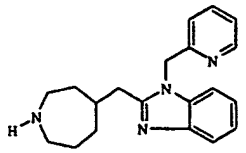
A mixture of intermediate (4) (0.021 mol) and KOH (0.43 mol) in 2-propanol (100ml) was stirred and refluxed overnight. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. Yield: 6.9g of compound (4) (quant.).

Example B4

Preparation of  (compound 5)

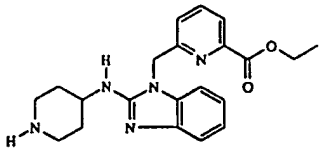
A mixture of intermediate (6) (0.02 mol) in ethanol (120ml) was hydrogenated with Pd/C 10% (2g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated, yielding a residue of 8g (100%). Part of this fraction (0.7g) was dissolved in ethanol and converted into the hydrochloric acid salt (1:3) with 2-propanol/HCl. DIPE was added. The mixture was stirred. The precipitate was filtered off and dried. Yield: 0.65g of compound (5).

Example B5

Preparation of  (compound 6)

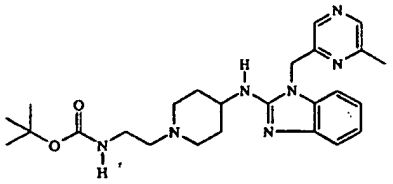
A mixture of intermediate (9) (0.035 mol) in methanol (200ml) was hydrogenated at room temperature under a 3 bar pressure for 48 hours with Pd/C (1.5g) as a catalyst, then hydrogenation was continued at 40°C under a 3 bar pressure for 48 hours. After uptake of H_2 (2 equiv), the catalyst was filtered through celite and the filtrate was evaporated. The residue (12g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 80/20/3). The pure fractions were collected and the solvent was evaporated. Yield: 3.8g of compound (6) (34%).

Example B6

Preparation of  (compound 7)

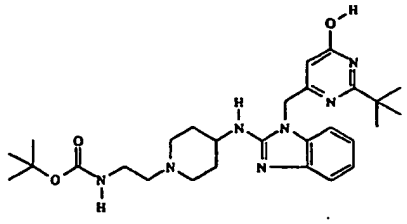
A mixture of 6-[[2-(4-piperidinylamino)-1*H*-benzimidazol-1-yl]methyl]-2-pyridine-carboxylic acid in HCl 36% (5ml) and ethanol (50ml) was stirred and refluxed overnight. The solvent was evaporated. H_2O, $NaHCO_3$ and CH_2Cl_2 were added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 90/10). The pure fractions were collected and the solvent was evaporated. Yield: 0.83g of compound (7).

Example B7

Preparation of  (compound 8)

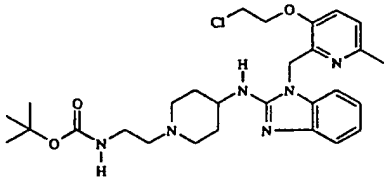
A mixture of compound (1) (0.003 mol), 1,1-dimethylethyl (2-bromoethyl) carbamoate (0.004 mol) and Na_2CO_3 (0.004 mol) in 2-butanone (100 ml) was stirred and refluxed overnight. The reaction mixture was cooled, washed with water and the layers were separated. The organic phase was washed with a NH_4Cl solution. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$ 97/3). The pure fractions were collected and the solvent was evaporated. Yield: a residue of 1.18 g of compound (8) (84%).

Example B8

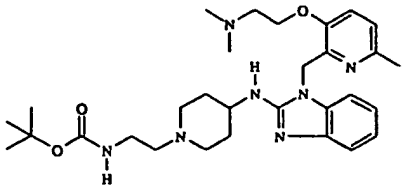
Preparation of  (compound 9)

Reaction under N_2 flow. NaH (0.01 mol) was added to a mixture of 1,1-dimethylethyl [2-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]ethyl]carbamate (0.01 mol) in DMF p.a. dry (100ml). The mixture was stirred at room temperature for 4 hours. 6-chloro-methyl-2-(1,1-dimethylethyl)-4-pyrimidinol (0.01 mol) in a small amount of DMF p.a. dry was added dropwise. The mixture was stirred at 50°C overnight and then cooled. H_2O (50ml) was added. The solvent was evaporated. The residue was taken up in CH_2Cl_2. The organic solution was washed with H_2O/HOAc, dried ($MgSO_4$), filtered and the solvent was evaporated, to give residue 1. The aqueous layer was taken up in HOAc and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, to give residue 2. Residue 1 and 2 were combined and purified by column chromatography over RP 18 BDS (eluent: NH_4OAc (0.5% in H_2O)/ CH_3OH/CH_3CN 70/15/15, 0/50/50 and 0/0/100). The pure fractions were collected and the solvent was evaporated. Yield: compound (9).

Example B9

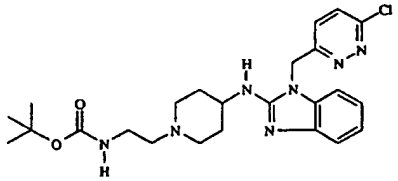
a) Preparation of  (compound 10)

Thionyl chloride (0.03 mol) was added to a mixture of (±)-6-methyl-3-[2-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethoxy]-2-pyridinemethanol (0.015 mol) in CH_2Cl_2 (100ml). Toluene was added and evaporated again. The residue was taken up in DMF (50ml) and then added to a mixture of 1,1-dimethylethyl [2-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]ethyl]carbamate (0.015 mol) and NaH (0.06 mol) in DMF (200ml). The mixture was stirred at 50°C overnight. The solvent was evaporated. The residue was taken up in H_2O and CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/ (CH_3OH/NH_3) 99/1). The pure fractions were collected and the solvent was evaporated. The residue was suspended in petroleum ether. The precipitate was filtered off and dried. Yield: 1.55g of compound (10) (20%).

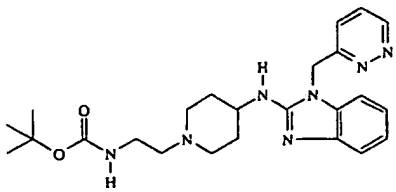
b) Preparation of  (compound 11)

A mixture of compound (10) (0.00147 mol) and $NH(CH_3)_2$ gas (20g) in THF (100ml) was stirred at 125°C for 16 hours. The solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/(CH_3OH/NH_3) 95/5). The pure fractions were collected and the solvent was evaporated. Yield: 0.43g of compound (11) (53%).

Example B10

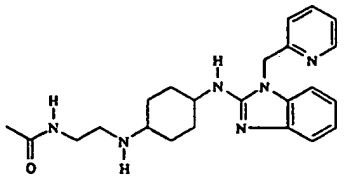
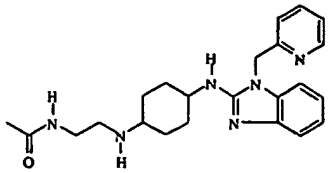
a) Preparation of  (compound 12)

1-Bromo-2,5-pyrrolidinedione (0.088 mol) and then dibenzoyl peroxide (cat.quant.) were added to a solution of 3-chloro-6-methylpyridazine (0.08 mol) in CCl_4 (mol. sieves) (200ml). The mixture was stirred and refluxed for 6 hours and then filtered over dicalite. 1-Bromo-2,5-pyrrolidinedione (0.088 mol) and dibenzoyl peroxide (cat.quant.) were added again. The mixture was stirred and refluxed overnight and filtered over dicalite. The solvent was evaporated at a temperature below 40°C. The residue was dissolved in DMF (70ml) and added to a mixture of 1,1-dimethylethyl [2-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]ethyl]carbamate (0.0214 mol) and NaH (0.0235 mol) in DMF (190ml), previously stirred at room temperature for 1 hour and at 40°C for 1 hour. The resulting mixture was stirred at 50°C overnight. The solvent was evaporated. H_2O and CH_2Cl_2 were added. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 97/3). The pure fractions were collected and their solvents were evaporated. Yield: 1.21g of compound (12).

b) Preparation of  (compound 13)

A mixture of compound (12) (0.0025 mol), CaO (2g) and Pd/C (1g) in 1-butanethiol (2ml) and THF (100ml) was stirred at room temperature for the weekend. The solvent was evaporated. Yield: 1g of compound (13) (88%).

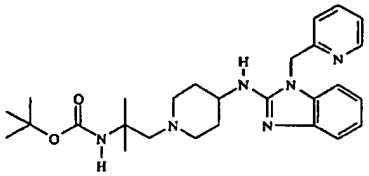
Example B11

Preparation of  and 

(cis) (compound 14) (trans) compound (15)

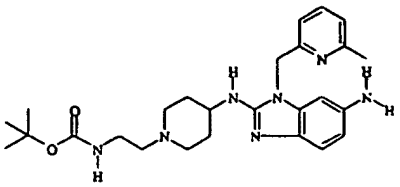
A mixture of intermediate (15) (0.031 mol) and *N*-(2-aminoethyl)acetamide (0.093 mol) in methanol (300ml) was hydrogenated at 30°C under a 3 bar pressure for 12 hours with Pd/C (5g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered through celite, washed with CH_3OH and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ CH_3OH/NH_4OH 92/8/0.5; 20-45 µm). Two pure fractions were collected and their solvents were evaporated, yielding a residue of 2.8g (22%) and 9g (71%). Parts of these fractions (0.6g; 0.8g) were crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 0.52g of compound (14); mp. 126°C and 0.53g of compound (15); mp. 200°C.

Example B12

Preparation of  (compound 16)

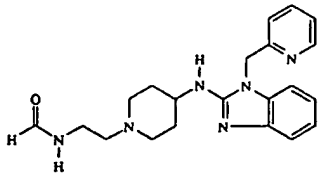
$NaBH_3CN$ (0.048 mol) was added portionwise at 5°C to a solution of *N*-4-piperidinyl-1-(2-pyridylmethyl)-1*H*-benzimidazol-2-amine dihydrochloride (0.032 mol) and 1,1-dimethylethyl (1,1-dimethyl-2-oxoethyl)carbamoate (0.032 mol) in methanol (100ml). The mixture was stirred at room temperature for 8 hours and hydrolized at 5°C with ice water. Methanol was evaporated. The residue was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (13g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 95/5/0.1; 20-45 µm). The pure fractions were collected and the solvent was evaporated. Yield : 2.2g of compound (16) (14%).

Example B13

Preparation of  (compound 17)

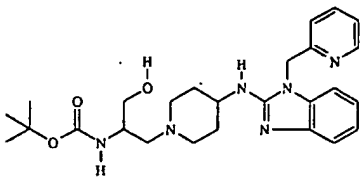
A mixture of 1,1-dimethylethyl [2-[4-[[1-[(6-methyl-2-pyridyl)methyl]-6-nitro-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (0.0084 mol) in methanol (150ml) was hydrogenated at 50°C with Pt/C 5% (1g) as a catalyst in the presence of thiophene solution (1ml). After uptake of H_2 (3 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 99/1 to 97.5/2.5). The pure fractions were collected and the solvent was evaporated. Yield: 3.3g of compound (17) (82%).

Example B14

Preparation of  (compound 18)

A mixture of *N*-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-pyridyl)methyl]-1*H*-benzimidazol-2-amine (0.143 mol) in HCOOH (50ml) was stirred and refluxed for 3 hours. The solvent was evaporated till dryness. The residue was dissolved in CH_2Cl_2. The mixture was basified with Na_2CO_3, filtered and the filtrate was evaporated till dryness. The residue (4.9g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/NH_4OH 92/8/1; 20-45 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanone. The precipitate was filtered off and dried. Yield: 2.8g of compound (18) (51%); mp. 146°C.

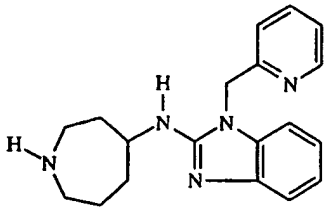
Example B15

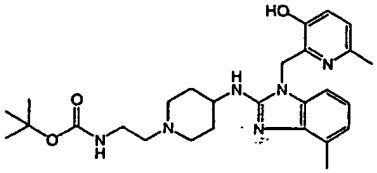
Preparation of  (compound 19)

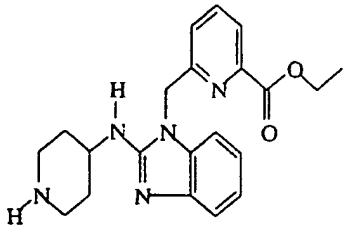
$LiAlH_4$ (0.0065 mol) was added portionwise at 5°C to a solution of (±)-1,1-dimethylethyl [1-(methoxycarbonyl)-2-[4-[[1-(2-pyridylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (0.0059 mol) in THF (30ml). The mixture was stirred at 5°C for 1 hour. EtOAc was added. The mixture was hydrolized with ice water, filtered over celite and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (2.8g) was purified by column

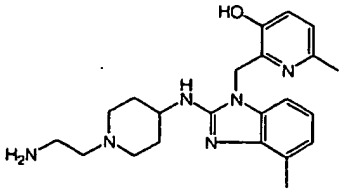
chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/ NH_4OH$ 92/8/0.5; 15-40 µm). The pure fractions were collected and the solvent was evaporated. Yield: 1.55g of compound (19) (56%).

Example B16

a) Preparation of  (compound 290)

A mixture of  (0.021mol) in 2-propanol/HCl (29 ml) and 2-propanol (290 ml) was stirred and refluxed for 2 hours and then cooled to room temperature. The precipitate was filtered off and combined with analogously obtained fraction. The precipitate was dissolved at reflux in ethanol (150 ml), then allowed to crystallize out. The precipitate was filtered off and dried (45 °C, 16 hours, then air-dried for 30 minutes). Yield: 8.9 g (70%) of compound (290). Compound (290) was converted into the free base according to art known procedures resulting in compound (355).

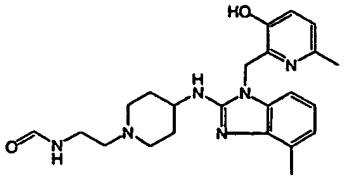
b) Preparation of  (compound 356) and

preparation of  (compound 357).

Hydroxybutanedioate (1:1) Hydrate (1:2)

Compound (355) (0.001 mol) was added to ethanol (6 ml; absolute ethanol) and heated to reflux temperature to give an homogeneous solution (I). Solution (I) was treated with butanedioic acid (0.118 g, 0.001 mol) and resulted in immediate salt formation. The mixture was heated to reflux temperature, became homogeneous, then was allowed to

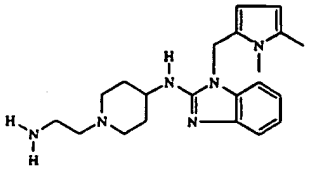
cool to room temperature. The precipitate was filtered off, and dried (vacuum, 50 °C, 24 hours). Yield: 0.40 g (78%) of compound (356). Solution (I) was treated with hydroxybutanedioic acid (0.134 g, 0.001 mol) and the mixture was heated to reflux temperature, became homogeneous, then was allowed to cool to room temperature. The precipitate was filtered off and dried (vacuum, 50 °C, 24 hours). Yield: 0.46 g (87%) of compound (357).

c) Preparation of  (compound 354)

Compound (290) (0.000065 mol) was dissolved in water (3 ml). The mixture was stirred and alkalized with concentrated NH_4OH (400 µl, and 100 µl). $CHCl_3$ (20 ml) was added. The mixture was stirred vigorously for 10 minutes. More conc. NH_4OH (100 µl) was added and the mixture was stirred vigorously for 5 minutes. The organic layer was separated, then the alkalic layer was re-extracted once with $CHCl_3$ (5 ml). The combined organic layers were washed once with a saturated aqueous NaCl solution, then dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was stirred in HCOOH (20 ml) until complete dissolution (= after 2 minutes). Acetic acid anhydride (0.00213 mol) was added dropwise over 1 minute and the reaction mixture was stirred at room temperature. After 24 hours, more acetic acid anhydride (50 µl) was added and the reaction mixture was stirred for 15 minutes. More acetic acid anhydride (50 µl) was added to the reaction mixture. The whole was stirred for 2 hours 15 minutes on a 60 °C oil-bath, then stood over the weekend at room temperature. More acetic acid anhydride (1000 µl) was added to the reaction mixture. The whole was stirred for 30 minutes on a 60-70 °C oil-bath, then stirred overnight at room temperature. Again, the reaction mixture was stirred for 2.5 hours at 60 °C. More acetic acid anhydride (100 µl) was added and the reaction mixture was stirred for 45 minutes at 60 °C, then stood overnight at room temperature. Water (100 µl) was added to decompose remaining acetic acid anhydride. The solvent was evaporated (in vacuo at 60 °C). Toluene was added to the residue, then evaporated again (in vacuo, 60 °C). Xylene was added, then evaporated (in vacuo at 60 °C) to give (x). To a sample, water (3 drops) was added. NH_4OH (10 µl) was added. Water (5 drops) was added and the mixture was shaken vigorously to give (y). (x) and (y) were dissolved in $CH_2Cl_2/CH_3OH/(CH_3OH/NH_3)$ 84/12/4, then purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/(CH_3OH/NH_3)$ 84/12/4). The product fractions were collected and the solvent was evaporated. This fraction (0.185 g) was stirred in boiling

ethanol (± 10 ml), allowed to cool to room temperature, then Et_2O (10 ml) was added and the mixture was stirred for 15 minutes. The precipitate was filtered off by suction, rinsed with Et_2O, then air-dried for 3 hours, then dried further (high vacuum, 2 hours at room temperature, then air-dried overnight at room temperature). Yield: 0.153 g of compound (354).

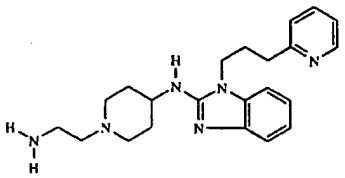
Example B17

Preparation of  (compound 21)

H_2O (1:1)

A mixture of 1,1-dimethylethyl [2-[4-[[1-(1,5-dimethyl-1*H*-pyrrol-2-yl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (0.002 mol) and KOH (1g) in sec. butanol (25ml) was stirred and refluxed for 1 hour. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was suspended in DIPE. The precipitate was filtered off and dried. Yield: 0.57g of compound (21).

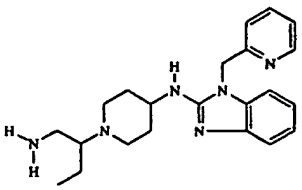
Example B18

Preparation of  (compound 22)

HCl (1:4); H_2O (1:2)

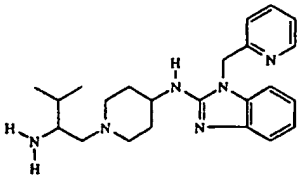
A mixture of 2-[2-[4-[[1-[3-(2-pyridyl)propyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-1*H*-isoindole-1,3(2*H*)-dione (0.005 mol) in HCl 6N (120ml) and HOAc (60ml) was stirred and refluxed for 30 hours and then cooled on an ice bath. A NaOH solution was added carefully dropwise until pH > 7. The mixture was extracted with CH_2Cl_2 and then separated into its layers. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, separated again, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was taken up in a small amount of 2-propanol and converted into the hydrochloric acid salt (1:4) with 2-propanol/HCl 6N. DIPE was added. The precipitate was filtered off, washed with DIPE and dried. Yield: 1.95g of compound (22) (70%).

Example B19

Preparation of  (compound 23)

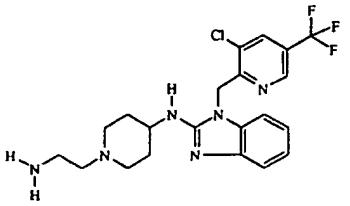
A mixture of intermediate (17) (0.01 mol) in hydrazine (5ml) and ethanol (50ml) was stirred and refluxed for 30 minutes. The solvent was evaporated. The residue was dissolved in CH_2Cl_2. The organic solution was washed with H_2O, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (4.8g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 89/10/1; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 51.7g of compound (23) (45%); mp. 112°C.

Example B20

Preparation of  (compound 24)

A mixture of 3-methyl-1-[4-[[1-(2-pyridylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-2-butanone (0.01 mol) and benzenemethanamine (0.031 mol) in methanol (50ml) was hydrogenated at 40°C under a 3 bar pressure for 24 hours with Pd/C (0.4g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered through celite, washed with CH_3OH and CH_2Cl_2 and the filtrate was evaporated. The residue (5g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 93/7/1; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from pentane. The precipitate was filtered off and dried. Yield: 1g of compound (24) (21%); mp. 115°C.

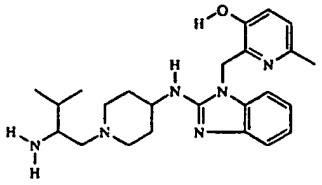
Example B21

Preparation of  (compound 25)

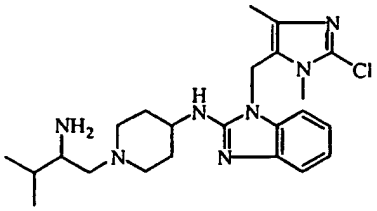
Reaction under N_2 atmosphere. Na_2CO_3 (0.250 g) was added to 1,1-dimethylethyl [2-[4-(1*H*-benzimidazol-2-ylamino)-1-piperidinyl]ethyl]carbamate (0.0028 mol) in DMF (10 ml). The mixture was stirred for 4 hours at room temperature. The reaction mixture was divided over 5 tubes. 2-Chloromethyl-3-chloro-5-trifluoropyridine

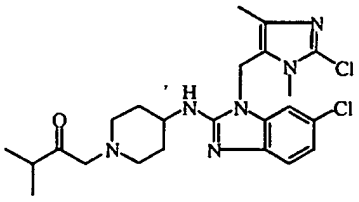
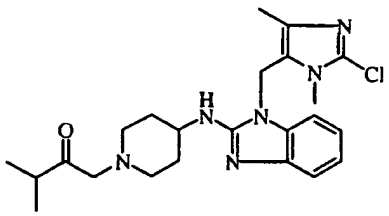
(0.100 g) was added to each tube and the resulting reaction mixture was stirred overnight at 50 °C. The mixture was acidified with HCl/2-propanol, then stirred for 3 hours at 90°C. The mixture was alkalized with NH_3/CH_3OH and the desired compound was isolated and purified by high-performance liquid chromatography over a Prochrom D.A.C.-column with Hypersil 'BDS' HS C18 (100 g, 8 µm, 100 Å; eluent gradient: ((0.5% NH_4OAc in H_2O)/CH_3OH/CH_3CN (0 min) 70/15/15, (10.31 min) 0/50/50, (16.32 min) 0/0/100, (16.33 min-end) 70/15/15). The desired fractions were collected and the solvent was evaporated. Yield: 0.020 g of compound (25).

Example B22

a) Preparation of  (compound 26)

A mixture of 1-[4-[[1-[(3-hydroxy-6-methyl-2-pyridyl)methyl]-1*H*-benzimidazol-2-yl]-amino]-1-piperidinyl]-3-methyl-2-butanone (0.0065 mol) in CH_3OH/NH_3 (300ml) was hydrogenated at room temperature with Rh/Al_2O_3 (1g) as a catalyst in the presence of CH_3OH/NH_3 (3ml). After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/(CH_3OH/NH_3) 95/5 to 90/10). The pure fractions were collected and the solvent was evaporated. Yield: 1.52g of compound (26) (55%).

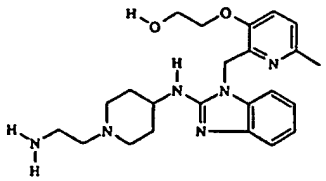
b) Preparation of  (compound 298)

A mixture (0.6g) of  and 

(prepared analogous to the procedure described in example A10b)) in NH_3/CH_3OH (100 ml) was hydrogenated for 16 hours at 50°C with Rh/C (0.5 g) as a catalyst in the presence of thiophene solution (1 ml). After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by high-performance liquid chromatography over Kromasil C18 (100 Å; eluent: NH_4OAc 0.5%

H_2O/CH_3CN 75%, 25% CH_3OH to CH_3CN 100%). Two pure fraction groups were collected and their solvent was evaporated. Yield : 0.165 g of compound 298.

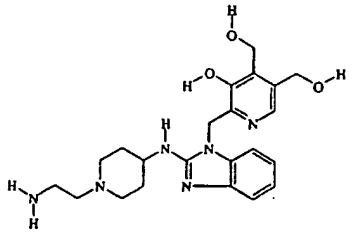
Example B23

Preparation of  (compound 27)

HCl (1:3); H_2O (1:1)

A mixture of (±)-1,1,dimethylethyl [2-[4-[[1-[[6-methyl-3-[2-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethoxy]-2-pyridyl]methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-carbamate (0.0014 mol) in 2-propanol/HCl (5ml) and 2-propanol (50ml) was stirred and refluxed for 4 hours and taken up in H_2O, Na_2CO_3 and CH_2Cl_2. The organic layer was separated. 2-Propanol/HCl (5ml) and 2-propanol (50ml) were added again. The mixture was stirred and refluxed for 1 hour and converted into the hydrochloric acid salt. The precipitate was filtered off and dried. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/ (CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was converted into the hydrochloric acid salt. The precipitate was filtered off and dried. Yield: 0.18g of compound (27) (23%).

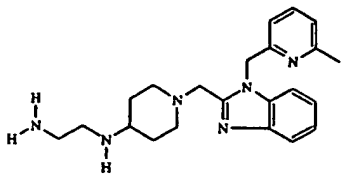
Example B24

Preparation of  (compound 28)

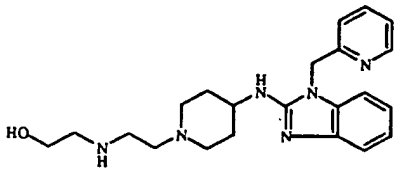
HCl (1:1)

A mixture of 1,1-dimethylethyl [2-[4-[[1-[[3,5-dihydro-3,3-dimethyl-9-(phenyl-methoxy)-1*H*-[1,3]dioxepino[5,6-c]pyridin-2-yl]methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]carbamate (0.00213 mol) in HCl 10N (100ml) was stirred and refluxed for 4 hours. The solvent was evaporated. The residue was suspended in DIPE. The precipitate was filtered off and dried. Yield: 0.9g of compound (28).

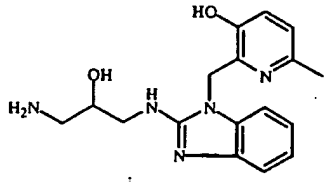
Example B25

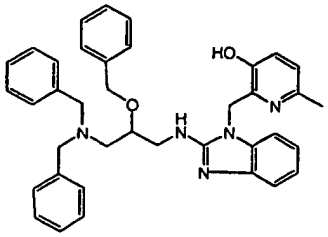
a) Preparation of  (compound 29)

A mixture of intermediate (19) (0.008 mol) in methanol (150ml) was hydrogenated with Pd/C (1g) as a catalyst. After uptake of H_2 (1 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH_2Cl_2/ (CH_3OH/NH_3) 95/5, 93/7 to 90/10). The pure fractions were collected and the solvent was evaporated. Yield: 1.81g of compound (29) (60%).

b) Preparation of  (compound 312)

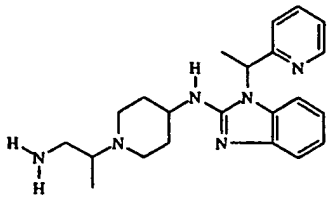
A mixture of intermediate (24) (0.011 mol) in methanol (100ml) was hydrogenated at room temperature under a 3 bar pressure overnight with Pd/C (2g) as a catalyst. The catalyst was recuperated and hydrogenation was continued at room temperature under a 3 bar pressure for 2 hours with Pd/C (2g) as a catalyst. After uptake of hydrogen (1 equiv), the catalyst was filtered off, washed with CH_3OH and CH_2Cl_2 and the filtrate was evaporated. The residue (4.5g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 85/15/1 and 56/40/4; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from 2-propanol and diethyl ether. The precipitate was filtered off and dried. Yield: 1.8g of compound (312) (40%).

c) Preparation of  (compound 313)

A mixture of  (0.016 mol), prepared according to A5c), in methanol (250 ml) was hydrogenated with Pd/C 10% (2 g) as a catalyst. After uptake of hydrogen (3 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel

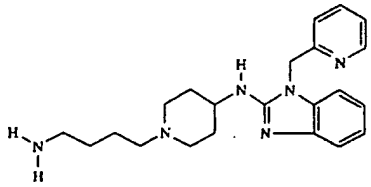
(eluent: CH_2Cl_2/(CH_3OH/NH_3) 90/10). The product fractions were collected and the solvent was evaporated. Yield: 4.2 g of compound (313).

Example B26

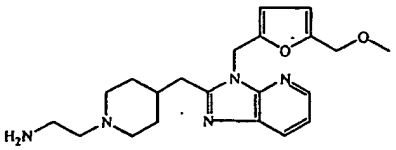
Preparation of  (compound 30)

$LiAlH_4$ (0.014 mol) was added portionwise at 5°C to a solution of intermediate (20) (0.012 mol) in THF (50ml). The mixture was allowed to warm to room temperature and then stirred at room temperature for 48 hours. EtOAc was added. The mixture was hydrolized with ice water, filtered over celite, washed with EtOAc and the filtrate was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (3g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH/ NH_4OH 87/13/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from DIPE. The precipitate was filtered off and dried. Yield: 0.75g of compound (30) (16%); mp. 85°C.

Example B27

a) Preparation of  (compound 31)

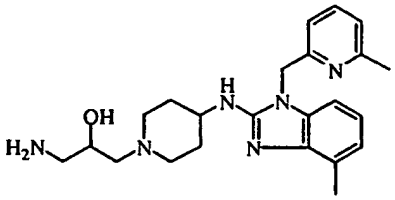
A mixture of 4-[[1-(2-pyridylmethyl)-1*H*-benzimidazol-2-yl]amino]-1-piperidine-butanenitrile (0.01 mol) in CH_3OH/NH_3 (80ml) was hydrogenated at room temperature under a 3 bar pressure overnight with Raney Nickel (3.8g) as a catalyst. After uptake of H_2 (2 equiv), the catalyst was filtered through celite and the filtrate was evaporated. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried. Yield: 2.9g of compound (31) (76%); mp. 94°C.

b) Preparation of  (compound 314)

A mixture of 5-[[2-[[1-(2-aminoethyl)-4-piperidinyl]methyl]-3H-imidazo[4,5-b]-pyridin-3-yl]methyl]-2-furanmethanol (0.0068 mol) in CH_3OH/NH_3 (300 ml) was

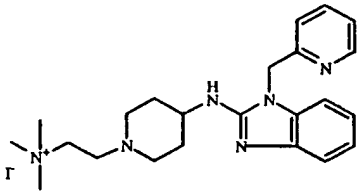
hydrogenated at 20 °C with Raney Nickel (1 g) as a catalyst. After uptake of H_2 (2 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) from 95/5 to 90/10). The desired fractions were collected and the solvent was evaporated. The residue was repurified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 95/5). The purest fractions were collected and the solvent was evaporated. The residue was taken up into HCl/2-propanol and DIPE was added. The resulting salt was filtered off and purified by column chromatography over silica gel (eluent: CH_2Cl_2/(CH_3OH/NH_3) 98/2). The pure fractions were collected and the solvent was evaporated. Yield: 0.2 g of compound (314).

Example B28

Preparation of  (compound 303)

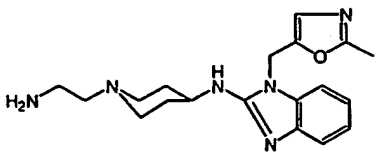
A mixture of intermediate 21 (0.001 mol) in CH_3OH/NH_3 (100ml) was stirred at room temperature for 20 hours and at 100°C for 16 hours. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ (CH_3OH/NH_3) 90/10). The pure fractions were collected and the solvent was evaporated. The residue was dried. Yield: 0.11g of compound 303.

Example B29

Preparation of  (compound 315)

Iodomethane (0.00494 mol) was added at room temperature to a solution of compound (328) (0.004491 mol) in 2-propanone (17ml), and the reaction mixture was stirred at room temperature for 1 hour. The precipitate was filtered off and dried. The residue (1.6g) was crystallized from 2-propanone. The precipitate was filtered off and dried. Yield: 1.5g of compound (315) (64%).

Example B30

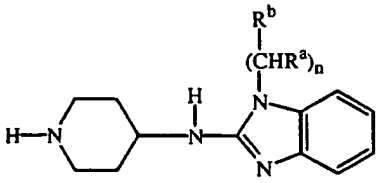
Preparation of  (compound 316)

Hydrochloride (1:3) Hydrate (1:1)

Compound (317) (0.0027 mol) was dissolved in ethanol (50ml). The mixture was converted into the hydrochloric acid salt (1:3) with 2-propanol/HCl. The precipitate was filtered off and dried. Yield: 1.68g of compound (316).

Tables 1 to 17 list the compounds of formula (I') and the compounds of group (I'') which were prepared according to one of the above examples.

Table 1

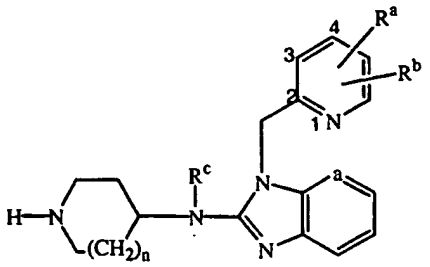


Co. No.	Ex. No.	n	R^a	R^b	Physical data
32	B1a	1	H	1,4-dimethyl-1*H*-imidazol-5-yl	H_2O (1:2)
33	B1a	1	H	1,4-dimethyl-5-[-$COOC_2H_5$]-1*H*-imidazol-2-yl	HCl (1:3)
34	B1a	1	H	2-bromo-5-pyridyl	
35	B1a	1	CH_3	2-pyrazinyl	
36	B1a	1	ethyl	2-pyrazinyl	
37	B1a	1	H	2-pyridyl	HCl (1:2); mp. >160°C
38	B1a	1	CH_3	2-pyridyl	
39	B1a	2	H	2-pyridyl	HCl (1:3); H_2O (1:2)
40	B1b	2	H	2-pyridyl	
41	B1b	3	H	2-pyridyl	HBr (1:3)
42	B1a	0	-	2-pyrimidinyl	
43	B1a	1	H	2-pyrimidinyl	HCl (1:3); H_2O (1:1)
44	B1a	1	H	3,5,6-trimethyl-2-pyrazinyl	
45	B1a	1	H	3-[C_2H_5-O-$(CH_2)_2$-O]-6-methyl-2-pyridyl	HCl (1:3); H_2O (1:3)
46	B1a	1	H	3-amino-2-pyridyl	HCl (1:3); H_2O (1:2)

Co. No.	Ex. No.	n	R^a	R^b	Physical data
47	B1a	1	H	3-amino-2-pyridyl	
48	B1a	1	H	3-hydroxy-2-pyridyl	HCl (1:3); H_2O (1:1)
49	B1a	1	H	3-hydroxy-6-methyl-2-pyridyl	HCl (1:3); H_2O (1:3)
50	B1a	1	H	3-hydroxy-6-pyridazinyl	HCl (1:2); H_2O (1:1)
51	B1a	1	H	3-methoxy-6-methyl-2-pyridyl	HCl (1:3); H_2O (1:2)
52	B1a	1	H	3-methoxy-6-methyl-2-pyridyl	
53	B1a	1	H	3-methyl-2-pyrazinyl	
3	B2b	1	H	3-OH-4,5-(-CH_2-OH)$_2$-2-pyridyl	HCl (1:3); H_2O (1:2)
54	B1a	1	H	3-pyridazinyl	
55	B3	1	H	1,5-$(CH_3)_2$-1*H*-pyrrol-2-yl	
56	B1a	1	H	4,6-dimethyl-2-pyridyl	
57	B1a	1	H	4-chloro-2-pyridyl	
58	B1a	1	H	4-methoxy-2-pyridyl	
59	B1a	1	H	4-methyl-1*H*-imidazol-5-yl	HCl (1:3); H_2O (1:1)
60	B1a	1	H	4-pyridyl	HCl (1:3); H_2O (1:1)
61	B1a	1	H	4-pyridyl	
62	B1a	1	H	4-pyrimidinyl	
63	B1a	1	H	5-chloro-1-methyl-1*H*-imidazol-2-yl	
64	B1a	1	H	5-methyl-2-pyrazinyl	HCl (1:1)
65	B1a	1	H	5-methyl-2-pyrazinyl	
66	B1a	1	H	6-(-CH_2-O-CH_3)- 2-pyridyl	HCl (1:2); H_2O (1:3)
67	B1a	1	H	6-(hydroxymethyl)-2-pyridyl	
68	B1a	1	H	6-[-CO-N$(CH_3)_2$]-2-pyridyl	
69	B1a	1	H	6-bromo-2-pyridyl	HCl (1:2)
70	B1a	1	H	6-bromo-2-pyridyl	
71	B1a	1	H	6-chloro-2- pyridyl	HCl (1:2)
72	B1a	1	H	6-HOOC-2-pyridyl	
73	B1a	1	CH_3	6-hydroxymethyl-2-pyridyl	HCl (1:3); H_2O (1:1)
74	B1a	1	H	6-methoxy-2-pyridyl	
1	B1a	1	H	6-methyl-2-pyrazinyl	
75	B1a	1	CH_3	6-methyl-2-pyrazinyl	
2	B2a	1	H	6-methyl-3-[-O-$(CH_2)_2$-OH]-2-pyridyl	HCl (1:3); H_2O (1:2)
76	B1a	1	H	6-methyl-3-[-O-$(CH_2)_2$-N$(CH_3)_2$]-2-pyridyl	HCl (1:4); H_2O (1:1)

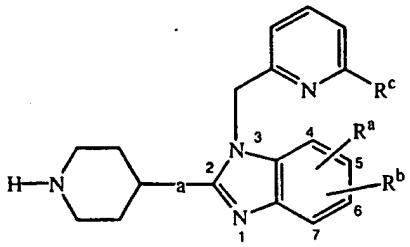
Co. No.	Ex. No.	n	R^a	R^b	Physical data
7	B6	1	H	6-(-$COOC_2H_5$)-2-pyridyl	

Table 2



Co. No.	Ex. No.	n	a	R^a	R^b	R^c	Physical data
78	B1a	1	CH	H	H	CH_3	-
4	B3	2	CH	H	H	H	-
81	B16	1	CH	H	H	-CH_2-phenyl	-
308	B1b	1	N	3-OH	6-CH_3	H	-

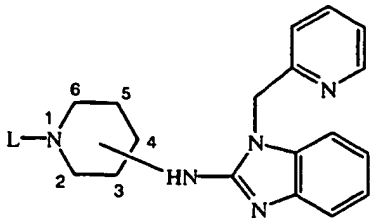
Table 3

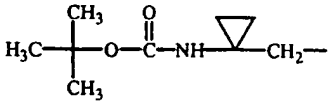
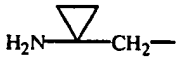


Co. No.	Ex. No.	a	R^a	R^b	R^c	Physical data
82	B4	CH_2	5-OCH_3	6-OCH_3	H	
83	B1b	NH	5-Cl	6-Cl	CH_3	HBr (1:3)
84	B1b	NH	5-CH_3	6-CH_3	CH_3	HBr (1:3)
85	B1b	NH	4-Cl	H	CH_3	HBr (1:3)
86	B1b	NH	7-Cl	H	CH_3	HBr (1:3); H_2O (1:1)
87	B1b	NH	6-NO_2	H	CH_3	HBr (1:3); H_2O (1:1)
88	B1b	NH	7-CH_3	H	CH_3	HBr (1:3)
89	B1b	NH	5-NO_2	H	CH_3	HBr (1:3); H_2O (1:1)
90	B1b	NH	7-CH_3	H	CH_3	
91	B1b	NH	4-CH_3	H	CH_3	HBr (1:3)
92	B1b	NH	4-CH_3	H	CH_3	

Co. No.	Ex. No.	a	R^a	R^b	R^c	Physical data
93	B1b	NH	5-CF_3	H	CH_3	
94	B1b	NH	6-CF_3	H	CH_3	
95	B1b	NH	6-Cl	H	CH_3	
96	B1b	NH	5-Cl	H	CH_3	
5	B4	NH	6-(-$COOC_2H_5$)	H	CH_3	
97	B4	NH	6-(-$COOC_2H_5$)	H	CH_3	HCl (1:3); H_2O (1:1)
98	B4	NH	6-(-CH_2-OH)	H	CH_3	HCl (1:3); H_2O (1:2)
99	B4	NH	6-(-CH_2-OH)	H	CH_3	
100	B1a	CH[$N(CH_3)_2$]	H	H	CH_3	HCl (1:4); H_2O (1:1)

Table 4



Co. No.	Ex. No.	*	L	Physical data
101	B4	4	3-piperidinyl	HCl (1:4); H_2O (1:2)
102	B4	3	H	
18	B14	4	-$(CH_2)_2$-NH-CHO	mp. 146°C
103	B7	4		
104	B16	4		HCl (1:4); H_2O (1:2); mp. 226°C
105	B16	4	-CH_2-$C(CH_3)_2$-NH_2	HCl (1:3); H_2O (1:2); mp. 195°C
106	B16	4	-CH_2-$CH(CH_2OH)$- NH_2	HCl (1:4); H_2O (1:2); mp. 200°C
23	B19	4	-$CH(C_2H_5)$-CH_2-NH_2	mp. 112°C
107	B19	4	-$CH(C_6H_5)$-$CH(C_6H_5)$-NH_2	(A); mp. 106°C
108	B19	4	-$CH(C_6H_5)$-$CH(C_6H_5)$-NH_2	(B); mp. 98°C
109	B19	4	2-aminocyclohexyl	mp. 116°C
110	B19	4	-CH(phenylmethyl)-CH_2-NH_2	mp. 168°C
111	B19	4	-$CH[C(CH_3)_3]$-CH_2-NH_2	mp. 133°C
112	B19	4	-$CH[CH_2$-$N(CH_3)_2]$-CH_2-NH_2	mp. 112°C
113	B19	4	-CH_2-$CH(NH_2)$-phenyl	mp. 128°C

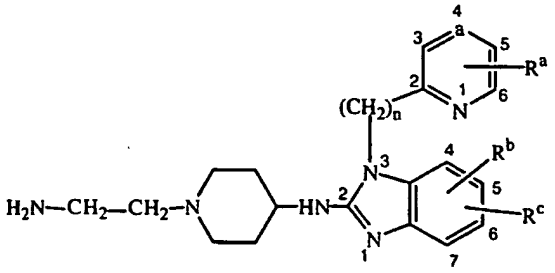
Co. No.	Ex. No.	*	L	Physical data
114	B19	4	-CH[CH_2-(1-piperidinyl)]-CH_2-NH_2	HCl (1:4); mp. 203°C
115	B19	4	-CH_2-CH(cyclopropyl)-NH_2	H_2O (1:2); mp. 84°C
24	B20	4	-CH_2-CH[$CH(CH_3)_2$]-NH_2	mp. 115°C
116	B20	4	-CH_2-$CH(CH_3)$-NH_2	H_2O (1:1)
117	B20	4	-$CH(CH_3)$-$CH(CH_3)$-NH_2	(B); mp. 114°C
118	B20	4	-CH_2-$CH(C_2H_5)$-NH_2	mp. 140°C
119	B20	4	-CH_2-CH(cycloC_6H_{11})-NH_2	mp. 134°C
120	B20	4	-$CH(CH_3)$-$CH(CH_3)$-NH_2	(A); HCl (1:4); H_2O (1:4); mp. 214°C
121	B20	4	-CH_2-$CH(NH_2)$-CH_2-$CH(CH_3)_2$	mp. 124°C
122	B20	4	-CH_2-$CH(NH_2)$-$(CH_2)_3$-CH_3	mp. 142°C
123	B20	4	-CH_2-$CH(NH_2)$-$(CH_2)_2$-$CH(CH_3)_2$	mp. 152°C
124	B20	4	-CH_2-$CH(NH_2)$-$(CH_2)_2$-CH_3	mp. 146°C
125	B20	4	-CH_2-$CH(NH_2)$-$(CH_2)_7$-CH_3	mp. 136°C
126	B20	4	-CH_2-$CH(NH_2)$-$(CH_2)_2$-phenyl	mp. 136°C
127	B20	4	-CH_2-$CH(NH_2)$-CH_2-$C(CH_3)_3$	HCl (1:4); H_2O (1:1); mp. 244°C
128	B20	4	-CH_2-$CH(NH_2)$-$CH(CH_3)(C_2H_5)$	(A); H_2O (1:1); mp. 80°C
129	B20	4	-CH_2-$CH(NH_2)$-$CH(CH_3)(C_2H_5)$	(B); mp. 90°C
130	B20	4	-CH_2-$CH(NH_2)$-$(CH_2)_2$-(4-methoxyphenyl)	mp. 100°C
131	B1a	4	-CH_2-$CH(NH_2)$-(4-piperidinyl)	HCl (1:5); H_2O (1:1); mp. 269°C
31	B27a	4	-$(CH_2)_4$-NH_2	mp. 94°C
132	B27a	4	-$CH(CH_3)$-CH_2-NH_2	mp. 142°C
133	B27a	3	-$(CH_2)_2$-NH_2	H_2O (1:1); mp. 90°C
134	B16	4	-$(CH_2)_3$-NH_2	HCl (1:4); H_2O (1:1); mp. >250°C
328	B7	4	-$(CH_2)_2$-$N(CH_3)_2$	-
327	B7	4	-$(CH_2)_2$-$N(CH_3)_2$	HCl (1:4); H_2O (1:3); mp. 180°C

* = position piperidinyl

(A) indicates the first isolated stereoisomeric form

(B) indicates the second isolated stereoisomeric form

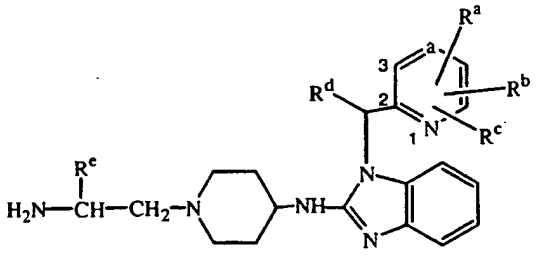
Table 5



Co. No.	Ex. No.	n	a	R^a	R^b	R^c	Physical data
135	B1a	1	CH	6-[-$COOCH(CH_3)_2$]	H	H	
136	B1a	1	CH	6-[-$COOC_2H_5$]	H	H	
137	B16	1	CH	6-CH_2OH	H	H	
138	B16	1	CH	6-CH_3	5-Cl	6-Cl	HCl (1:4); H_2O (1:1)
139	B16	1	N	3-CH_3	H	H	HCl (1:3); H_2O (1:1)
20	B16	1	N	6-CH_3	H	H	HCl (1:3); H_2O (1:2)
140	B16	1	N	5-CH_3	H	H	HCl (1:4); H_2O (1:2)
141	B16	2	CH	H	H	H	HCl (1:4); H_2O (1:1)
142	B16	1	CH	6-CH_3	5-CH_3	6-CH_3	HCl (1:4); H_2O (1:2); 2-propanolate (1:1)
143	B16	1	CH	6-CH_3	4-Cl	H	HCl (1:4); H_2O (1:2)
144	B16	1	CH	6-CH_3	7-Cl	H	HCl (1:4); H_2O (1:2)
145	B16	1	CH	6-CH_3	6-NO_2	H	HCl (1:4); H_2O (1:3)
146	B16	1	CH	6-CH_3	6-NH_2	H	HCl (1:5); H_2O (1:2)
147	B16	1	CH	6-CH_3	5-NO_2	H	HCl (1:4); H_2O (1:1)
148	B16	1	CH	6-CH_3	5-NH_2	H	HCl (1:5); H_2O (1:1)
149	B16	1	CH	6-CH_3	7-CH_3	H	
151	B16	1	CH	6-Cl	H	H	
153	B16	1	CH	6-Br	H	H	
154	B16	1	CH	6-OH	H	H	
155	B16	1	CH	6-OCH_3	H	H	
156	B16	1	CH	4-Cl	H	H	HCl (1:4); H_2O (1:1)
157	B16	1	CH	4-OCH_3	H	H	HCl (1:4); H_2O (1:2); 2-propanolate (1:1)
158	B16	1	CH	6-CH_2OCH_3	H	H	HCl (1:4); H_2O (1:2)
159	B16	1	N	5-$COOC_2H_5$	H	H	HCl (1:3); H_2O (1:1)
160	B16	1	CH	6-CH_3	4-CH_3	H	HCl (1:4); H_2O (1:2)
161	B16	1	CH	6-CH_3	6-$COOC_2H_5$	H	HCl (1:4); H_2O (1:1)

Co. No.	Ex. No.	n	a	R^a	R^b	R^c	Physical data
162	B16	1	CH	6-CH_3	6-CH_2OH	H	H_2O (1:1)
163	B16	1	CH	6-CH_3	5-CF_3	H	HCl (1:4); H_2O (1:2)
164	B16	1	CH	6-CH_3	6-CF_3	H	HCl (1:4); H_2O (1:1)
165	B16	1	CH	6-$CON(CH_3)_2$	H	H	HCl (1:3); H_2O (1:2)
166	B16	1	CH	6-CH_3	5-Cl	H	HCl (1:4); H_2O (1:2)
22	B18	3	CH	H	H	H	HCl (1:4); H_2O (1:2)
167	B27a	1	CH	6-CH_3	H	H	
305	B16	1	CH	6-CH_3	5-CH_3	H	-
306	B16	1	CH	6-CH_3	6-Cl	H	HCl (1:4)

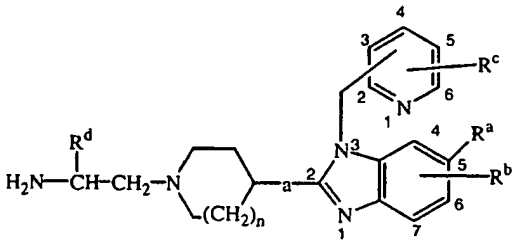
Table 6



Co. No.	Ex. No.	a	R^a	R^b	R^c	R^d	R^e	Physical data
168	B27a	CH	3-OH	H	H	H	H	-
169	B1a	CH	3-[-O-$(CH_2)_2$-$N(CH_3)_2$]	6-CH_3	H	H	H	HCl (1:5); H_2O (1:2)
152	B16	CH	H	H	H	CH_3	H	HCl (1:4); H_2O (1:3)
170	B20	CH	3-NH_2	H	H	H	$CH(CH_3)_2$	HCl (1:4); H_2O (1:3)
171	B20	N	5-CH_3	H	H	H	CH_3	mp. 175°C
172	B20	N	6-CH_3	H	H	H	CH_3	mp. 126°C
173	B20	N	3-CH_3	5-CH_3	6-CH_3	H	CH_3	HCl (1:4); H_2O (1:3); mp. 208°C
174	B20	N	3-CH_3	5-CH_3	6-CH_3	H	$CH(CH_3)_2$	mp. 124°C
175	B16	N	H	H	H	CH_3	H	HCl (1:3)
176	B16	N	3-CH_3	5-CH_3	6-CH_3	H	H	HCl (1:4); H_2O (1:1); 2-propanolate (1:1)
177	B16	N	H	H	H	ethyl	H	HCl (1:3); H_2O (1:1)
178	B16	N	6-CH_3	H	H	CH_3	H	HCl (1:3); H_2O (1:1)
179	B16	CH	4-CH_3	6-CH_3	H	H	H	HCl (1:4); H_2O (1:2)
180	B16	CH	6-Cl	H	H	CH_3	H	HCl (1:3); H_2O (1:1)
181	B16	CH	3-OH	6-CH_3	H	H	H	HCl (1:3); H_2O (1:2)

Co. No.	Ex. No.	a	R^a	R^b	R^c	R^d	R^e	Physical data
182	B16	CH	3-OCH_3	6-CH_3	H	H	H	
183	B16	CH	6-CH_2OH	H	H	CH_3	H	HCl (1:4); H_2O (1:1)
184	B16	CH	3-[O-$(CH_2)_2$-OC_2H_5	6-CH_3	H	H	H	HCl (1:4); H_2O (1:2)
185	B16	CH	3-OCH_2CH_2Cl	6-CH_3	H	H	H	HCl (1:3); H_2O (1:2)
186	B20	CH	H	H	H	CH_3	CH_3	HCl (1:3); H_2O (1:3); mp. 170°C
187	B20	N	6-CH_3	H	H	H	$CH(CH_3)_2$	HCl (1:3); H_2O(1:3); mp. 200°C
188	B20	CH	H	H	H	CH_3	$CH(CH_3)_2$	mp. 233°C
189	B20	N	5-CH_3	H	H	H	$CH(CH_3)_2$	mp. 114°C
190	B20	CH	H	H	H	H	$CH(CH_3)_2$	mp. 50°C
25	B21	CH	3-Cl	5-CF_3	H	H	H	
26	B22a	CH	3-OH	6-CH_3	H	H	$CH(CH_3)_2$	
27	B23	CH	3-O-$(CH_2)_2$-OH	6-CH_3	H	H	H	HCl (1:3); H_2O(1:1)
28	B24	CH	4-CH_2OH	3-OH	5-CH_2OH	H	H	HCl (1:1)
192	B27a	CH	6-CH_3	H	H	CH_3	H	
299	B16	CH	3-CN	H	H	H	H	mp. 142°C
300	B20	CH	4-OCH_3	3-OCH_3	H	H	$CH(CH_3)_2$	HCl (1:4); H_2O(1:2); mp. 210°C
301	B16	CH	3-NH-SO_2-pheny	6-Cl	H	H	H	mp. 161°C
307	B20	CH	5-OCH_3	6-OCH_3	H	H	$CH(CH_3)_2$	$C_2H_2O_4$ (2:7); mp. 90°C

Table 7

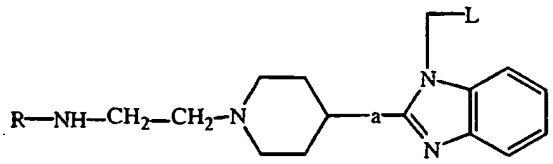


Co. No.	Ex. No.	n	*	a	R^a	R^b	R^c	R^d	Physical data
193	B16	2	2	CH_2	H	H	H	H	ethanedioate (1:3); H_2O (1:2); mp. 125°C
194	B22b	1	2	NH	Cl	H	6-CH_3	$CH(CH_3)_2$	
195	B22b	1	2	NH	H	7-CH_3	6-CH_3	$CH(CH_3)_2$	
196	B16	2	2	NH	H	H	H	H	ethanedioate (2:7); H_2O (1:2); mp. 170°C

Co. No.	Ex. No.	n	*	a	R^a	R^b	R^c	R^d	Physical data
197	B16	1	2	$N(CH_3)$	H	H	H	H	
198	B16	1	2	$N(CH_2$-phenyl)	H	H	H	H	HCl (1:3); H_2O (1:1)
199	B27a	0	2	NH	H	H	H	H	HCl (1:4); H_2O (1:2)
200	B1a	1	2	CH_2	OCH_3	6-OCH_3	H	H	HCl (1:4); H_2O (1:1); 2-propanolate (1:1)
201	B1a	1	3	NH	H	H	6-Br	H	HBr (1:4); H_2O (1:4)
202	B16	1	4	NH	H	H	H	H	HCl (1:4); H_2O (1:3)
296	B22b	1	2	NH	CH_3	H	6-CH_3	$CH(CH_3)_2$	-

* = position pyridyl

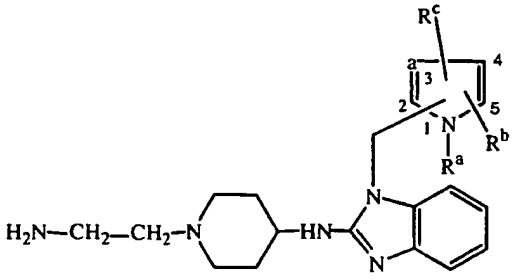
Table 8



Co. No.	Ex. No.	L	a	R	Physical data
203	B16	4-pyrimidinyl	NH	H	HCl (1:4); H_2O (1:2)
204	B16	2-pyrimidinyl	NH	H	HCl (1:3); H_2O (1:1)
205	B16	2-pyrimidinyl	NH	H	
206	B16	3-pyridazinyl	NH	H	HCl (1:3); H_2O (1:1)
207	B16	4,6-dimethoxy-2-pyrimidinyl	NH	H	HCl (1:4); H_2O (1:3)
208	B16	2-pyrimidinyl	NH	H	HCl (1:4); H_2O (1:1)
209	B16	6-methyl-2-pyridyl	$CH[N(CH_3)_2]$	H	HCl (1:4); H_2O (1:2); 2-propanolate (1:1)
210	B7	6-methyl-2-pyridyl	$CH[N(CH_3)_2]$	$-COOC(CH_3)_3$	
211	B25a	2-pyridiyl	NH	CH_3	HCl (1:4); H_2O (1:2); mp. 224°C
212	B27a	2-[$C(CH_3)_3$]-6-OH-4-pyrimidinyl	NH	H	
320	B30	2-pyridinyl	NH	H	HCl (1:4); H_2O (1:1)
319	B27a	2,4-dimethyl-5-oxazolyl	NH	H	
329	B16	2,5-dimethyl-4-oxazolyl	NH	H	HCl (1:3); H_2O (1:1)
333	B16	5-methyl-3-isoxazolyl	NH	H	HCl (1:3); H_2O (1:1)
317	B27a	2-methyl-5-oxazolyl	NH	H	mp. 115°C; H_2O (1:1)
323	B27a	4-thiazolyl	NH	H	
326	B16	5-phenyl-1,2,4-oxadiazol-3-yl	NH	H	HCl (1:3)

Co. No.	Ex. No.	L	a	R	Physical data
332	B16	2-(hydroxymethyl)-5-oxazolyl	NH	H	HCl (1:4); H_2O (1:2)
331	B16	3-methyl-5-isoxazolyl	NH	H	HCl (1:3); H_2O (1:1)
324	B16	2-(dimethylamino)-4-thiazolyl	CH_2	H	HCl (1:4); H_2O (1:1); propanolate (1:1)
325	B27a	2-methyl-4-thiazolyl	CH_2	H	
318	B27a	2-methyl-3-furanyl	NH	H	mp. 142°C
312	B25b	2-pyridinyl	NH	CH_2-CH_2OH	mp. 151°C
316	B30	2-methyl-5-oxazolyl	NH	H	HCl (1:4);H_2O(1:1)

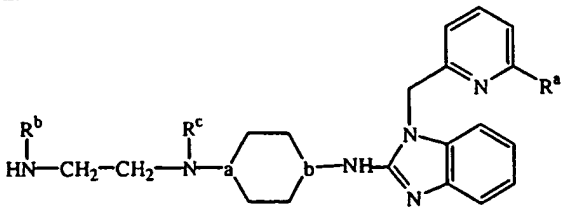
Table 9



Co. No.	Ex. No.	*	a	R^a	R^b	R^c	Physical data
213	B16	2	N	$CH_2C_6H_5$	H	H	HCl (1:4)
214	B16	5	N	H	4-CH_3	H	HCl (1:4); H_2O (1:3)
215	B16	5	N	CH_3	4-CH_3	H	HCl (1:4); H_2O (1:2)
216	B16	2	N	CH_3	5-$COOC_2H_5$	4-CH_3	HCl (1:4)
217	B16	2	N	CH_3	5-Cl	H	HCl (1:4); H_2O (1:2)
218	B16	5	N	2-propyl	2-SCH_3	H	HCl (1:4); H_2O (1:1)
219	B16	5	N	C_2H_5	2-CH_3	4-CH_3	HCl (1:4); H_2O (1:2); 2-propanolate (1:1)
220	B16	5	N	CH_3	2-CH_3	4-CH_3	HCl (1:4); H_2O (1:2)
21	B17	2	CH	CH_3	5-CH_3	H	H_2O (1:1)
221	B27a	2	CH	CH_3	5-$COOC_2H_5$	H	
222	B27a	2	CH	CH_3	5-$COOC_2H_5$	4-Br	

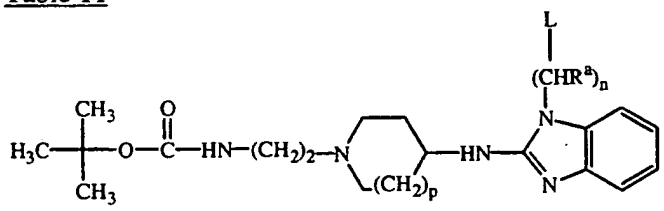
* position monocyclic heterocycle

Table 10



Co. No.	Ex. No.	a	b	R^a	R^b	R^c	Physical data
14	B11	CH	CH	H	$COCH_3$	H	(cis); mp. 126
15	B11	CH	CH	H	$COCH_3$	H	(trans); mp. 200
223	B16	CH	CH	H	H	H	(trans); HCl (1:4); H_2O (1:1); mp. 210
29	B25a	CH	N	CH_3	H	H	
224	B25a	CH	N	CH_3	H	CH_3	HCl (1:5); H_2O (1:3)

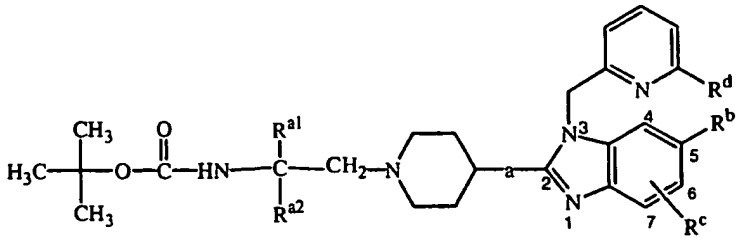
Table 11



Co. No.	Ex. No.	n	p	R^a	L	Physical data
225	B7	1	1	H	6-chloro-2-pyridyl	
8	B7	1	1	H	6-methyl-2-pyrazinyl	
226	B7	1	2	H	2-pyridyl	
227	B7	1	1	H	5-methyl-2-pyrazinyl	
228	B7	1	1	CH_3	2-pyridyl	
229	B7	1	2	H	2-pyridyl	
230	B7	1	1	H	4-methyl-1*H*-imidazol-5-yl	
231	B7	1	1	H	3-methyl-2-pyrazinyl	
232	B7	2	1	H	2-pyridyl	
233	B7	1	1	H	1,4-dimethyl-1*H*-imidazol-5-yl	
234	B7	1	1	H	4-pyrimidinyl	
235	B7	0	1	-	2-pyrimidinyl	
236	B7	1	1	H	6-(hydroxymethyl)-2-pyridyl	
237	B7	1	1	H	1,4-dimethyl-5-(-$COOC_2H_5$)-1*H*-imidazol-2-yl	

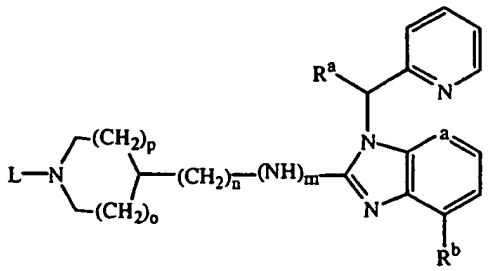
Co. No.	Ex. No.	n	p	R^a	L	Physical data
238	B7	1	1	CH_3	2-pyrazinyl	
239	B7	1	1	H	3,5,6-trimethyl-2-pyrazinyl	
240	B7	1	1	Ethyl	2-pyrazinyl	
241	B7	1	1	CH_3	6-methyl-2-pyrazinyl	
242	B7	1	1	H	5-chloro-1-methyl-1*H*-imidazol-2-yl	
243	B7	1	1	H	4,6-dimethyl-2-pyridyl	
244	B7	1	1	H	6-bromo-2-pyridyl	
245	B7	1	1	H	6-(-$COOC_2H_5$)-2-pyridyl	
246	B7	1	1	H	1,5-dimethyl-2-pyrrolyl	
247	B7	1	1	H	6-methoxy-2-pyridyl	
248	B7	1	1	H	4-chloro-2-pyridyl	
249	B7	1	1	H	4-methoxy-2-pyridyl	
250	B7	1	1	H	2-pyrimidinyl	
251	B7	1	1	H	3-methoxy-6-methyl-2-pyridyl	
252	B7	1	1	H	6-methyl-3-(-O-C_2H_4-O-C_2H_5)-2-pyridyl	
253	B7	1	1	CH_3	6-hydroxymethyl-2-pyridyl	
254	B7	1	1	H	6-bromo-3-pyridyl	
9	B8	1	1	H	2-(1,1-dimethylethyl)-6-hydroxy-4-pyrimidinyl	
255	B8	1	1	H	1-(phenylmethyl)-1*H*-imidazol-2-yl	
256	B8	1	1	H	1-(2-propyl)-2-(-S-CH_3)-1*H*-imidazol-5-yl	
257	B8	1	1	CH_3	6-chloro-2-pyridyl	
258	B8	1	1	H	1-ethyl-2,4-dimethyl-1*H*-imidazol-5-yl	H_2O (1:1)
259	B8	1	1	H	3-hydroxy-6-methyl-2-pyridyl	
260	B8	1	1	H	4,6-dimethoxy-2-pyrimidinyl	
261	B8	1	1	H	5-(-$COOC_2H_5$)-2-pyrazinyl	
262	B8	1	1	H	1,2,4-trimethyl-1*H*-imidazol-5-yl	
10	B9a	1	1	H	3-(-O-C_2H_4Cl)-6-methyl-2-pyridyl	
263	B9a	1	1	H	6-(-CH_2-O-CH_3)-2-pyridyl	
11	B9b	1	1	H	3-[-O-C_2H_4-N(CH_3)$_2$]-6-methyl-2-pyridyl	
12	B10a	1	1	H	6-chloro-3-pyridazinyl	
13	B10b	1	1	H	3-pyridazinyl	
330	B7	1	1	H	2-methyl-4-methoxycarbonyl-5-oxazolyl	

Table 12



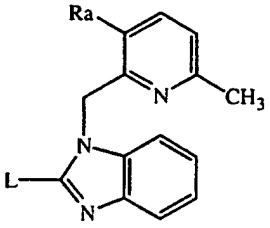
Co. No.	Ex. No.	R^{a1}, R^{a2}	R^b	R^c	a	R^d	Physical data
264	B7	H, H	OCH_3	6-OCH_3	CH_2	H	
265	B7	H, H	H	H	$N(CH_3)$	H	
266	B7	H, H	H	H	$N(CH_2-C_6H_5)$	H	
267	B7	H, H	Cl	6-Cl	NH	CH_3	
268	B7	H, H	CH_3	6-CH_3	NH	CH_3	
269	B7	H, H	H	4-Cl	NH	CH_3	
270	B7	H, H	H	7-Cl	NH	CH_3	
271	B7	H, H	H	6-NO_2	NH	CH_3	
272	B7	H, H	NO_2	H	NH	CH_3	
273	B7	H, H	H	7-CH_3	NH	CH_3	
274	B7	H, H	H	4-CH_3	NH	CH_3	H_2O (1:1)
275	B7	H, H	H	6-ethoxy-carbonyl	NH	CH_3	
276	B7	H, H	H	6-hydroxy-methyl	NH	CH_3	
277	B7	H, H	CF_3	H	NH	CH_3	
278	B7	H, H	H	6-CF_3	NH	CH_3	
279	B7	H, H	H	H	NH	-CO-$N(CH_3)_2$	
280	B7	H, H	Cl	H	NH	CH_3	
16	B12	CH_3, CH_3	H	H	NH	H	
17	B13	H, H	$-NH_2$	H	NH	CH_3	
281	B13	H, H	H	6-NH_2	NH	CH_3	
19	B15	$-CH_2OH$, H	H	H	NH	H	

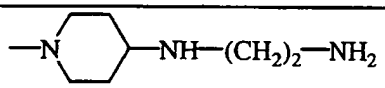
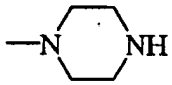
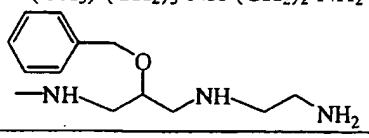
Table 13



Co. No.	Ex. No.	n	m	o	p	a	R^a	R^b	L	Physical data
6	B5	1	0	2	1	CH	H	H	H	
283	B27a	1	0	1	1	N	H	H	$-(CH_2)_2-NH_2$	HCl (1:4), H_2O (1:1); 2-propanolate (1:1)
284	B27a	1	1	1	1	N	H	H	$-(CH_2)_2-NH_2$	HCl (1:1)
285	B27a	1	1	0	2	CH	H	H	$-(CH_2)_2-NH_2$	HCl (1:4), H_2O (1:1); mp. 205°C
286	B4	1	1	0	2	CH	H	H	H	
30	B26	0	1	1	1	CH	CH_3	H	$-CH(CH_3)-CH_2-NH_2$	mp. 85°C

Table 14



Co. No.	Ex. No.	R_a.	L	Physical data
288	B25a	H		
289	B4	H		
309	B19	H	$-NH-(CH_2)_3-NH_2$	HCl (1:3); H_2O (1:2)
347	B16	H	$-NH-CH(CH_3)-(CH_2)_2-NH-(CH_2)_2-NH_2$	HCl(1:4); 2-propanolate (1:1)
345	B19	H	$-N(CH_3)-(CH_2)_3-NH-(CH_2)_2-NH_2$	HCl (1:4); H_2O (1:1)
346	B19	H		HCl (1:4); H_2O (1:1)

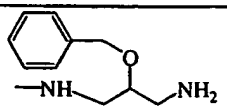
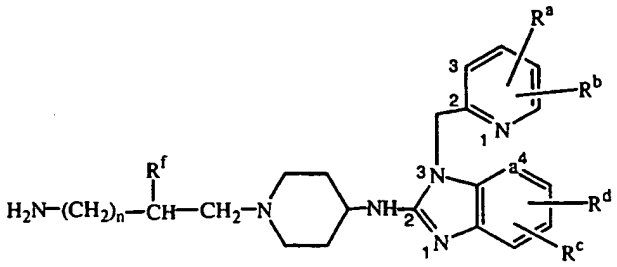
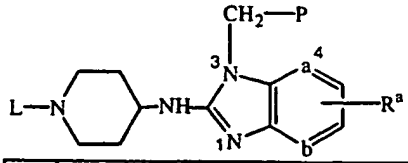
Co. No.	Ex. No.	R_a.	L	Physical data
341	B25a	H		HCl (1:3); H_2O (1:1)
313	B25c	OH	$-NHCH_2CH(OH)CH_2NH_2$	

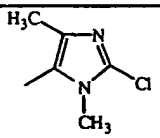
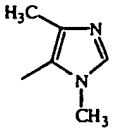
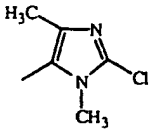
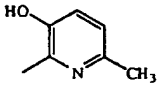
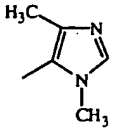
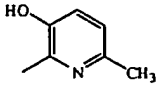
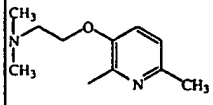
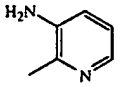
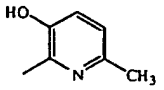
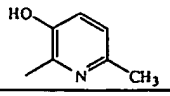
Table 15



Co. No.	Ex. No.	a	n	R^a	R^b	R^c	R^d	R^f	Physical data
290	B16	CH	0	3-OH	6-CH_3	7-CH_3	H	H	HCl (1:4);H_2O (1:4)
291	B22b	N	0	3-OH	6-CH_3	7-CH_3	H	CH-$(CH_3)_2$	-
292	B22b	CH	0	3-OH	6-CH_3	7-CH_3	H	CH_3	HCl (1:4);H_2O (1:3)
293	B22b	CH	0	3-OH	6-CH_3	7-CH_3	H	CH-$(CH_3)_2$	-
195	B22b	CH	0	6-CH_3	H	7-CH_3	H	CH-$(CH_3)_2$	-
303	B28	CH	1	6-CH_3	H	7-CH_3	H	OH	H_2O (1:1)
304	B22b	CH	0	6-CH_3	H	6-CH_3	H	CH-$(CH_3)_2$	-
342	B16	CH	0	3-OH	6-CH_3	5-Cl	7-CH_3	H	HCl (1:4), 2-propanolate (1:1)
348	B16	CH	0	3-OH	6-CH_3	5-Br	7-CH_3	H	HCl (1:4)
351	B22b	CH	0	3-OH	6-CH_3	4-CH_3	H	CH-$(CH_3)_2$	HCl (1:4);H_2O (1:1)
340	B16	CH	0	3-OH	6-CH_3	4-CH_3	H	H	HCl (1:4);H_2O (1:2)
344	B16	CH	0	3-OH	6-CH_3	4-CH_3	6-Cl	H	HCl (1:4);H_2O (1:4)
349	B16	CH	0	3-OH	6-CH_3	5-(4-fluoro-benzoyl)	H	H	HCl (1:4);H_2O (1:2)
350	B16	CH	0	3-OH	6-CH_3	6-(4-fluoro-benzoyl)	H	H	HCl (1:4);H_2O (1:2)
355	B16	CH	0	3-OH	6-CH_3	7-CH_3	H	H	
356	B16	CH	0	3-OH	6-CH_3	7-CH_3	H	H	$C_4H_6O_4$(1:1);H_2O(1:1)
357	B16	CH	0	3-OH	6-CH_3	7-CH_3	H	H	$C_4H_6O_5$(1:1);H_2O(1:2)
353	B16	CH	0	3-OH	6-CH_3	7-CH_3	H	H	HCl(1:4);H_2O(1:5)

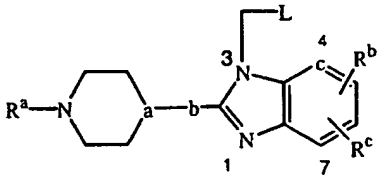
Table 16



Co. No.	Ex. No.	a	b	R^a	L	P	Physical data
295	B22b	CH	CH	5-Cl	$-CH_2-CH(NH_2)-CH(CH_3)_2$		
297	B22b	CH	CH	5-Cl	$-CH_2-CH(NH_2)-CH(CH_3)_2$		H_2O (1:1)
298	B22b	CH	CH	H	$-CH_2-CH(NH_2)-CH(CH_3)_2$		
310	B1b	CH	N	H	H		HBr (1:3).H_2O (1:1).C_2H_6O (1:1)
302	B1a	CH	CH	5-Cl	H		
321	B27a	N	CH	H	$-CH_2-CH_2-NH_2$	2,4-dimethyl-5-oxazolyl	
339	B8	N	CH	7-CH_3	$-C(=O)-O-CH_2-CH_3$		
336	B9b	CH	CH	H	$-C(=O)-O-C(CH_3)_3$		
337	B25a	CH	CH	H	$-C(=O)-O-CH_2-CH_3$		mp. 171°C
352	B7	CH	CH	7-CH_3	$-(CH_2)_3-NH-C(=O)OC(CH_3)_3$		
354	B16	CH	CH	7-CH_3	$-(CH_2)_3-NH-CH=O$		.HCl(1:4)

5

Table 17



Co. No.	Ex. No.	a	b	c	R^a	R^b	R^c	L	Physical data
343	B1b	CH	NH	CH	H	5-Br	7-CH_3	3-hydroxy-6-methyl-2-pyridinyl	HBr (1:3)
338	B1b	CH	NH	CH	H	H	7-CH_3	3-hydroxy-6-methyl-2-pyridinyl	
335	B20	N	NH	CH	$-CH_2-CH(CH(CH_3)_2)-NH_2$	H	H	2-pyridinyl	mp. 198°C
334	B27a	N	NH	CH	$-(CH_2)_2-NH_2$	H	H	2-pyridinyl	mp. 186
322	B27a	N	CH_2	N	$-(CH_2)_2-NH_2$	H	H	2-methyl-5-oxazolyl	
314	B27b	CH	CH_2	N	$-(CH_2)_2-NH_2$	H	H	5-methoxymethyl-2-furanyl	

C. Pharmacological example

Example C1 : In vitro screening for activity against Respiratory Syncytial Virus.

The percent protection against cytopathology caused by viruses (antiviral activity or IC_{50}) achieved by tested compounds and their cytotoxicity (CC_{50}) were both calculated from dose-response curves. The selectivity of the antiviral effect is represented by the selectivity index (SI), calculated by dividing the CC_{50} (cytotoxic dose for 50% of the cells) by the IC_{50} (antiviral activity for 50 % of the cells).

Automated tetrazolium-based colorimetric assays were used for determination of IC_{50} and CC_{50} of test compounds. Flat-bottom, 96-well plastic microtiter trays were filled with 180 µl of Eagle's Basal Medium, supplemented with 5 % FCS (0% for FLU) and 20 mM Hepes buffer. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45 µl volumes to a series of triplicate wells so as to allow simultaneous evaluation of their effects on virus- and mock-infected cells. Five five-fold dilutions were made directly in the microtiter trays using a robot system. Untreated virus controls, and HeLa cell controls were included in each test. Approximately 100 TCID50 of Respiratory Syncytial Virus was added to two of the three rows in a volume of 50 µl. The same volume of medium was added to the third row to measure the cytotoxicity of the compounds at the same concentrations as those used to measure the antiviral activity. After two hours of incubation, a suspension (4 x 10^5 cells/ml) of HeLa

cells was added to all wells in a volume of 50µl. The cultures were incubated at 37°C in a 5% CO_2 atmosphere. Seven days after infection the cytotoxicity and the antiviral activity was examined spectrophotometrically. To each well of the microtiter tray, 25 µl of a solution of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added . The trays were further incubated at 37°C for 2 hours, after which the medium was removed from each cup. Solubilization of the formazan crystals was achieved by adding 100 µl 2-propanol. Complete dissolution of the formazan crystals were obtained after the trays have been placed on a plate shaker for 10 min. Finally, the absorbances were read in an eight-channel computer-controlled photometer (Multiskan MCC, Flow Laboratories) at two wavelengths (540 and 690 nm). The absorbance measured at 690 nm was automatically subtracted from the absorbance at 540 nm, so as to eliminate the effects of non-specific absorption.

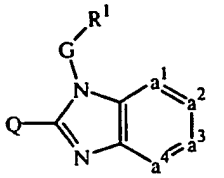
Particular IC_{50}, CC_{50} and SI values are listed in Table 18 hereinbelow.

Table 18

Co. No.	IC_{50} (µM)	CC_{50} (µM)	SI
290	0.00013	>0.010	>79
292	0.00032	63.85	199526
351	0.00063	50.04	79433
297	0.00251	>99.93	>39811
296	0.00631	19.95	3162
27	0.0126	>100.08	>7943
192	0.0631	63.1	1000
144	0.1259	50.11	398
222	0.5012	39.59	79
142	1.2589	40.28	32
145	2.5119	>50.24	>20

Claims

1. Use of a compound for the manufacture of a medicament for the treatment of viral infections, wherein the compound is a compound of formula



(I)

a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);

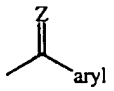
-N=CH-CH=CH- (a-2);

-CH=N-CH=CH- (a-3);

-CH=CH-N=CH- (a-4); or

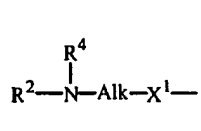
-CH=CH-CH=N- (a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula

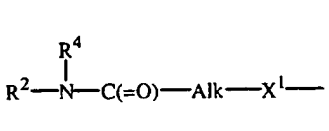


wherein =Z is =O, =CH-C(=O)-$NR^{5a}R^{5b}$, $=CH_2$, =CH-C_{1-6}alkyl, =N-OH or =N-O-C_{1-6}alkyl;

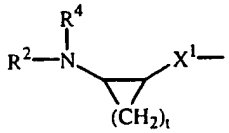
Q is a radical of formula



(b-1)



(b-2)



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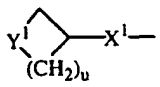
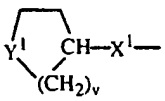


(b-4)



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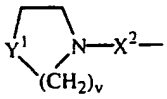
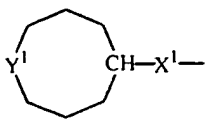
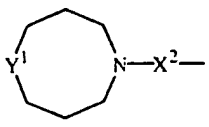


(b-6)



(b-7)



(b-8)

wherein Alk is C_{1-6}alkanediyl;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl;

t is 2, 3, 4 or 5;

u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8) may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl;

R^1 is a monocyclic heterocycle selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, and isothiazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, HO(-CH_2-CH_2-O)$_n$-, halo(-CH_2-CH_2-O)$_n$-, C_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$-, arylC_{1-6}alkyloxy(-CH_2-CH_2-O)$_n$- and mono-or di(C_{1-6}alkyl)amino(-CH_2-CH_2-O)$_n$-;

each n independently is 1, 2, 3 or 4;

R^2 is hydrogen, formyl, C_{1-6}alkylcarbonyl, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with $N(R^6)_2$, or C_{1-10}alkyl substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl or arylC_{1-6}alkyloxy;

R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;

R^{5a}, R^{5b}, R^{5c} and R^{5d} each independently are hydrogen or C_{1-6}alkyl; or

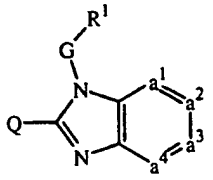
R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together form a bivalent radical of formula -$(CH_2)_s$- wherein s is 4 or 5;

R^6 is hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;

Het is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl.

2. A compound of formula (I')



(I')

a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a radical of formula

-CH=CH-CH=CH- (a-1);

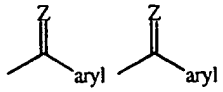
-N=CH-CH=CH- (a-2);

-CH=N-CH=CH- (a-3);

-CH=CH-N=CH- (a-4); or

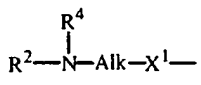
-CH=CH-CH=N- (a-5);

wherein each hydrogen atom in the radicals (a-1), (a-2), (a-3), (a-4) and (a-5) may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula

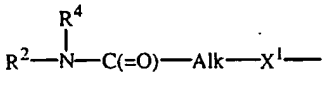


wherein =Z is =O, =CH-C(=O)-$NR^{5a}R^{5b}$, $=CH_2$, =CH-C_{1-6}alkyl, =N-OH or =N-O-C_{1-6}alkyl;

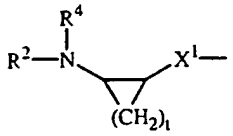
Q is a radical of formula



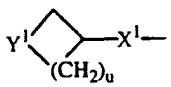
(b-1)



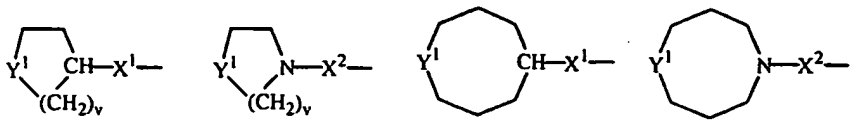
(b-2)



(b-3)



(b-4)



(b-5) (b-6) (b-7) (b-8)

wherein Alk is C_{1-6}alkanediyl;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl;

t is 2, 3, 4 or 5;

u is 1, 2, 3, 4 or 5;

v is 2 or 3; and

whereby each hydrogen atom in Alk and the carbocycles and the heterocycles defined in radicals (b-3), (b-4), (b-5), (b-6), (b-7) and (b-8) may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is a direct bond or C_{1-10}alkanediyl;

R^1 is a monocyclic heterocycle selected from pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, imidazolyl and pyrazolyl; and each heterocycle may optionally be substituted with 1 or where possible more, such as 2, 3 or 4, substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkyloxy, hydroxyC_{1-6}alkyl, mono-or di(C_{1-6}alkyl)amino, mono-or di(C_{1-6}alkyl)aminoC_{1-6}alkyl, polyhaloC_{1-6}alkyl, C_{1-6}alkyl-carbonylamino, C_{1-6}alkyl-SO_2-NR^{5c}-, aryl-SO_2-NR^{5c}-, C_{1-6}alkyloxycarbonyl, -C(=O)-$NR^{5c}R^{5d}$, $HO(-CH_2-CH_2-O)_n$-, halo$(-CH_2-CH_2-O)_n$-, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n$-, arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n$- and mono-or di(C_{1-6}alkyl)amino$(-CH_2-CH_2-O)_n$-;

each n independently is 1, 2, 3 or 4;

R^2 is hydrogen, formyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C_{3-7}cycloalkyl substituted with $N(R^6)_2$, or C_{1-10}alkyl substituted with $N(R^6)_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C_{3-7}cycloalkyl, C_{2-5}alkanediyl, piperidinyl, mono-or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, aryl and aryloxy;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl or arylC_{1-6}alkyloxy;

R^4 is hydrogen, C_{1-6}alkyl or arylC_{1-6}alkyl;

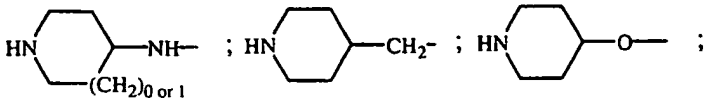
R^{5a}, R^{5b}, R^{5c} and R^{5d} each independently are hydrogen or C_{1-6}alkyl; or

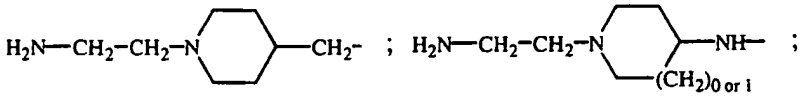
R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together form a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;

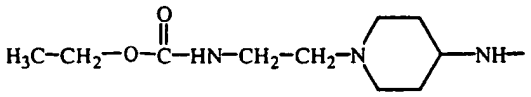
R^6 is hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, polyhaloC_{1-6}alkyl, and C_{1-6}alkyloxy;

provided that when G is methylene, and R^1 is 2-pyridyl, 3-pyridyl, 6-methyl-2-pyridyl, 2-pyrazinyl or 5-methyl-imidazol-4-yl, and $-a^1=a^2-a^3=a^4-$ is $-CH=CH-CH=CH-$ or $-N=CH-CH=CH-$, then Q is other than





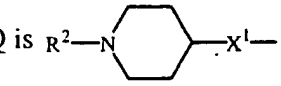


3. A compound as claimed in claim 2 wherein the following restrictions apply :

when Q is 

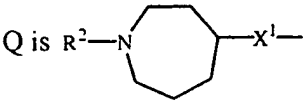
wherein X^1 is NR^4, O, S, S(=O), $S(=O)_2$, CH_2, C(=O), $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

4. A compound as claimed in claim 2 wherein the following restrictions apply :

when Q is 

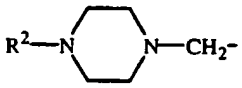
wherein X^1 is NR^4, O, S, S(=O), $S(=O)_2$, CH_2, C(=O), $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyridyl substituted with 1 or 2 C_{1-6}alkyloxy, pyrazinyl, pyrrolyl, pyrrolyl substituted with C_{1-6}alkyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

5. A compound as claimed in claim 2 wherein the following restrictions apply :

when Q is 

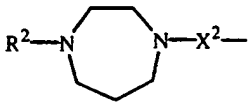
wherein X^1 is NR^4, O, S, S(=O), $S(=O)_2$, CH_2, C(=O), $C(=CH_2)$ or $CH(CH_3)$, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

6. A compound as claimed in claim 2 wherein the following restrictions apply :

when Q is 

then R^1 is other than pyridyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

7. A compound as claimed in claim 2 wherein the following restrictions apply :

when Q is 

wherein X^2 is CH_2 or a direct bond, then R^1 is other than pyridyl, pyridyl substituted with C_{1-6}alkyl, pyrimidinyl, pyrazinyl, imidazolyl and imidazolyl substituted with C_{1-6}alkyl.

8. A compound as claimed in claim 2 wherein the compound is selected from (±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-7-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride monohydrate; 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl]methyl-3-pyridinol; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(1,4-dimethyl-*1H*-imidazol-5-yl)methyl]-*1H*-benzimidazol-2-amine monohydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(6-methyl-2-pyridinyl)methyl]-*1H*-benzimidazol-2-amine; (±)-2-[[2-[(3-amino-2-hydroxypropyl)amino]-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[[3-(2-ethoxyethoxy)-6-methyl-2-pyridinyl]methyl]-*1H*-benzimidazol-2-amine tetrahydrochloride dihydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-chloro-1,4-dimethyl-*1H*-imidazol-5-yl)methyl]-*1H*-benzimidazol-2-amine; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(2-chloro-1,4-dimethyl-*1H*-imidazol-5-yl)methyl]-*1H*-benzimidazol-2-amine; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-methyl-1-[(6-methyl-2-pyridinyl)methyl]-*1H*-benzimidazol-2-amine; (±)-*N*-[1-(2-aminopropyl)-4-piperidinyl]-1-[(3,5,6-trimethylpyrazinyl)methyl]-*1H*-benzimidazol-2-amine tetrahydrochloride trihydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(3,5,6-trimethylpyrazinyl)methyl]-*1H*-benzimidazol-2-amine; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[[3-(2-chloroethoxy)-

6-methyl-2-pyridinyl]methyl]-*1H*-benzimidazol-2-amine trihydrochloride dihydrate; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[3-amino-2-pyridinyl)methyl]-*1H*-benzimidazol-2-amine tetrahydrochloride trihydrate; 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride; (±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-7-methyl-3*H*-imidazo[4,5-b]pyridin-3-yl]methyl]-6-methyl-3-pyridinol; 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-6-chloro-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride 2-propanolate (1:1); (±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol; (±)-2-[[2-[[1-(2-aminopropyl)-4-piperidinyl]amino]-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride trihydrate; 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-7-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride dihydrate; 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-6-bromo-4-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride; 2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride monohydrate; (±)-2-[[2-[[1-(2-amino-3-methylbutyl)-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol; (±)-*N*-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-4-methyl-1-[(6-methyl-2-pyridinyl)methyl]-*1H*-benzimidazol-2-amine;
a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex and stereochemically isomeric form thereof.

9. A compound selected from
2-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino]-5-chloro-7-methyl-*1H*-benzimidazol-1-yl]methyl]-6-methyl-3-pyridinol tetrahydrochloride tetrahydrate; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2,4-dimethyl-5-oxazolyl)methyl]-*1H*-benzimidazol-2-amine; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2,5-dimethyl-4-oxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate; 4-[[3-[[5-(methoxymethyl)-2-furanyl]methyl]-3*H*-imidazo[4,5-b]pyridine-2-yl]methyl]-1-piperidineetanamine; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(5-methyl-3-isoxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methyl-5-oxazolyl)methyl]-*1H*-benzimidazol-2-amine monohydrate; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methyl-5-oxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate; N-[1-(2-aminoethyl)-4-piperidinyl]-3-[(2,4-dimethyl-5-oxazolyl)methyl]-3H-imidazo[4,5-b]pyridin-2-amine; 4-[[3-[(2-methyl-5-

oxazolyl)methyl]-3H-imidazo[4,5-b]pyridin-2-yl]methyl]-1-piperazineethanamine; N-[1-(2-aminoethyl)-4-piperidinyl]-1-(4-thiazolylmethyl)-*1H*-benzimidazol-2-amine; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(5-phenyl-1,2,4-oxadiazol-3-yl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride; 5-[[2-[[1-(2-aminoethyl)-4-piperidinyl]amino-*1H*-benzimidazol-1-yl]methyl-2-oxazolemethanol tetrahydrochloride dihydrate; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(3-methyl-5-isoxazolyl)methyl]-*1H*-benzimidazol-2-amine trihydrochloride monohydrate; 4-[[1-[[2-(dimethylamino)-4-thiazolyl]methyl]-*1H*-benzimidazol-2-yl]methyl]-1-piperidineethanamine tetrahydrochloride monohydrate 2-propanolate (1:1); ethyl 5-[[2-[[1-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]-4-piperidinyl]amino]-*1H*-benzimidazol-1-yl]methyl]-2-methyl-4-oxazolecarboxylate; 4-[[1-[(2-methyl-4-thiazolyl)methyl]-*1H*-benzimidazol-2-yl]methyl]-1-piperidineethanamine; N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methyl-3-furanyl)methyl]-*1H*-benzimidazol-2-amine; ethyl 4-[[3-[(3-hydroxy-6-methyl-2-pyridinyl)methyl]-7-methyl-3H-imidazo[4,5-b]pyridine-2-yl]amino]-1-piperidinecarboxylate; 1,1-dimethylethyl 4-[[1-[[3-[2-(dimethylamino)ethoxy]-6-methyl-2-pyridinyl]methyl]-*1H*-benzimidazol-2-yl]amino-1-piperidinecarboxylate; ethyl 4-[[1-[(3-amino-2-pyridinyl)methyl]-*1H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate; N-[1-(6-methyl-2-pyridinyl)-*1H*-benzimidazol-2-yl]-1-(3-pyridinylcarbonyl)-4-piperidinamine;
a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex and stereochemically isomeric form thereof.

10. A compound as claimed in anyone of claims 2 to 9 for use as a medicine.

11. Use of a compound as claimed in claim 9 for the manufacture of a medicament for the treatment of viral infections.

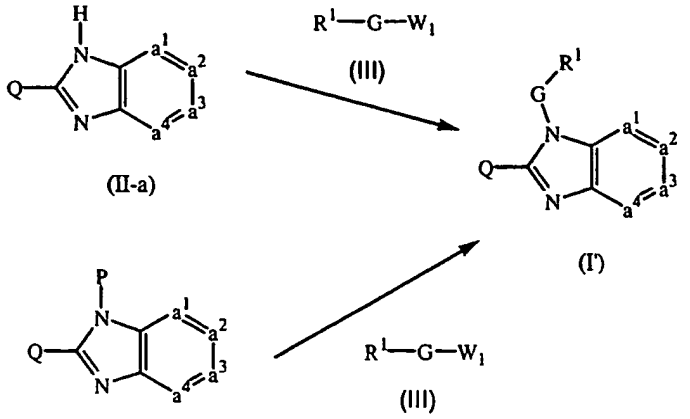
12. Use of a compound according to claim 1 or 11 wherein said viral infection is a respiratory syncytial virus infection.

13. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in claim 2 or claim 9.

14. A process of preparing a composition as claimed in claim 13 characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as claimed in claim 2 or claim 9.

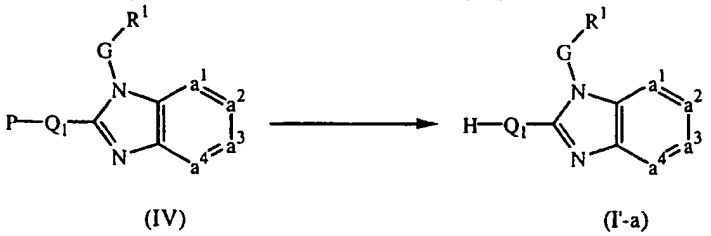
15. A process of preparing a compound as claimed in claim 2, characterized by

a) reacting an intermediate of formula (II-a) or (II-b) with an intermediate of formula (III)



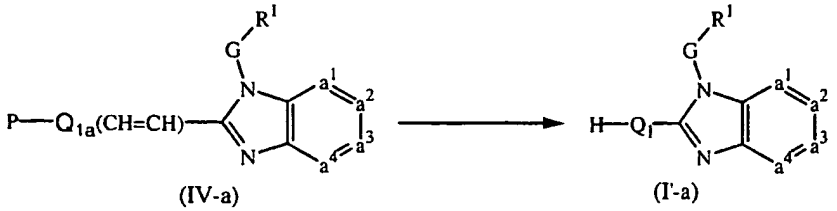
with R^1, G, Q and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and W_1 being a suitable leaving group, in the presence of a suitable base and in a suitable reaction-inert solvent;

b) deprotecting an intermediate of formula (IV)



with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, H-Q_1 being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is hydrogen, and P being a protective group;

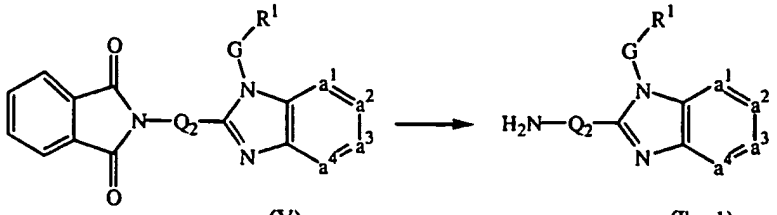
c) deprotecting and reducing an intermediate of formula (IV-a)



with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, H-Q_1 being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is hydrogen,

Q_{1a}(CH=CH) being defined as Q_1 provided that Q_1 comprises an unsaturated bond, and P being a protective group

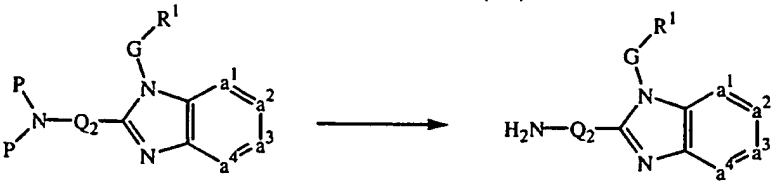
d) deprotecting an intermediate of formula (V)



(V) (I'-a-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H_2N-Q_2 being defined as Q according to claim 2 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen;

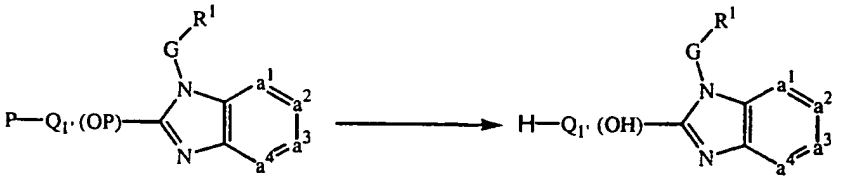
e) deprotecting an intermediate of formula (VI)



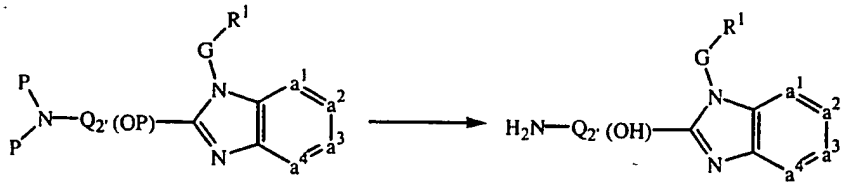
(VI) (I'-a-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H_2N-Q_2 being defined as Q according to claim 2 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and P being a protective group;

f) deprotecting an intermediate of formula (VII) or (VIII)



(VII) (I'-a-2)

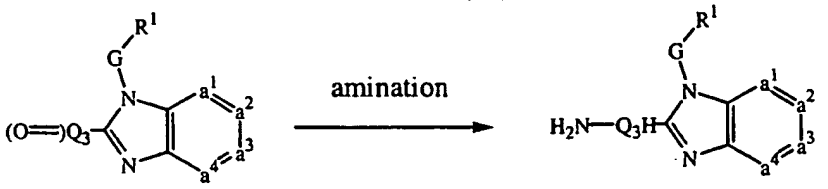


(VIII) (I'-a-1-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, $H-Q_{1'}(OH)$ being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is hydrogen and provided that Q comprises a hydroxy moiety, $H_2N-Q_{2'}(OH)$ being defined as Q

according to claim 2 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen and provided that Q comprises a hydroxy moiety, and P being a protective group;

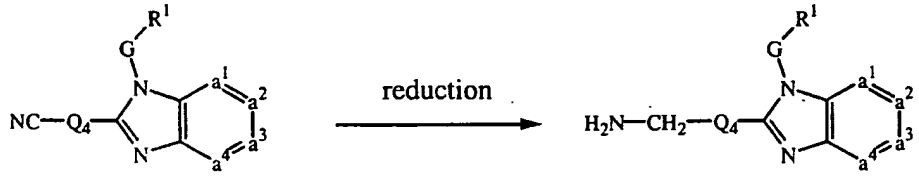
g) amination of an intermediate of formula (IX)



(IX) (I'-a-1-2)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H_2N-Q_3H being defined as Q according to claim 2 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6, or R^2 and R^4 substituents contains at least one hydrogen, in the presence of a suitable amination reagent;

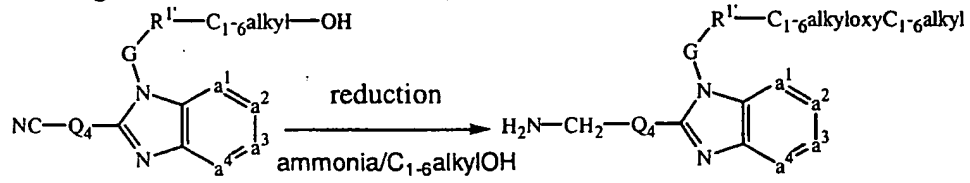
h) reducing an intermediate of formula (X)



(X) (I'-a-1-3)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $H_2N-CH_2-Q_4$ being defined as Q according to claim 2 provided that Q comprises a $-CH_2-NH_2$ moiety, in the presence of a suitable reducing agent;

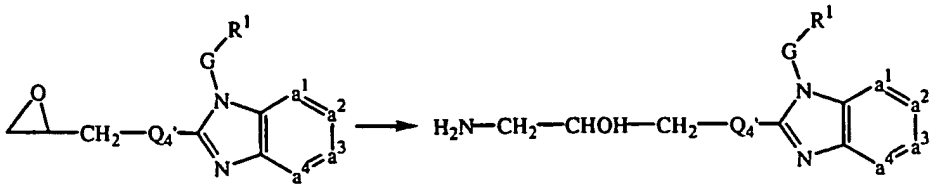
i) reducing an intermediate of formula (X-a)



(X-a) (I'-a-1-3-1)

with G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, $H_2N-CH_2-Q_4$ being defined as Q according to claim 2 provided that Q comprises a $-CH_2-NH_2$ moiety, and $R^{1'}$ being defined as R^1 according to claim 2 provided that it comprises at least one substituent, in the presence of a suitable reducing agent and suitable solvent;

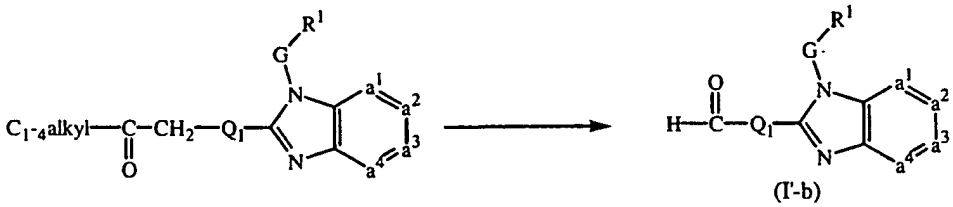
j) amination of an intermediate of formula (XI)



(XI) (I'-a-1-3-2)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $H_2N-CH_2-CHOH-CH_2-Q_4$, being defined as Q according to claim 2 provided that Q comprises a $CH_2-CHOH-CH_2-NH_2$ moiety, in the presence of a suitable amination reagent;

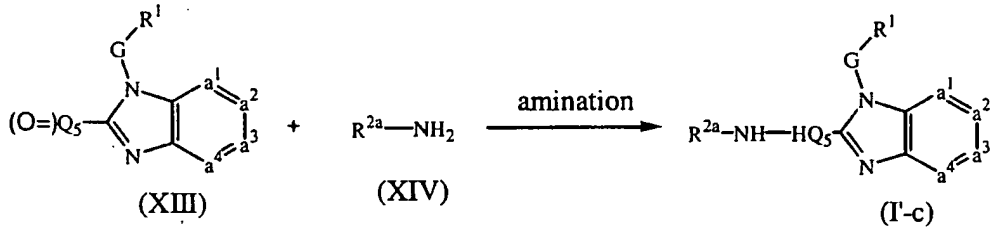
k) reacting an intermediate of formula (XII) with formic acid, formamide and ammonia



(XII) (I'-b)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $H-C(=O)-Q_1$ being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is formyl;

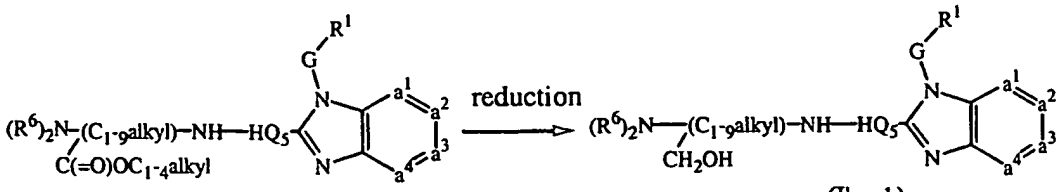
l) amination of an intermediate of formula (XIII) by reaction with an intermediate of formula (XIV)



(XIII) (XIV) (I'-c)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $R^{2a}-NH-HQ_5$ being defined as Q according to claim 2 provided that R^2 is other than hydrogen and is represented by R^{2a}, R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, in the presence of a suitable reducing agent;

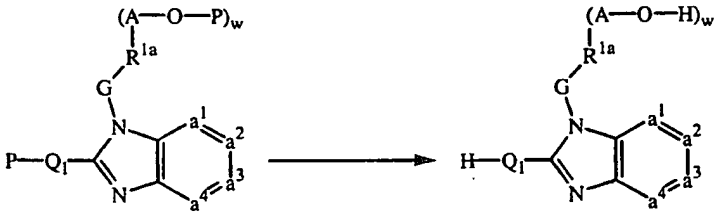
m) reducing an intermediate of formula (XV)



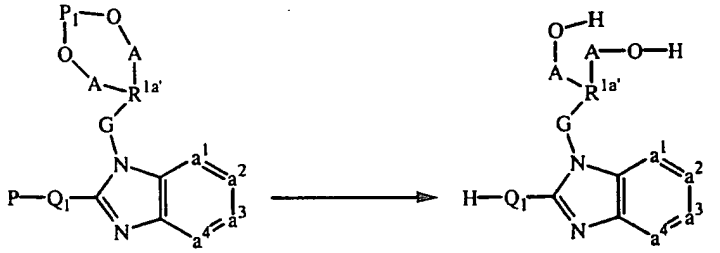
(XV) (I'-c-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and $(R^6)_2N$-[$(C_{1-9}$alkyl$)CH_2OH$]-NH-HQ_5 being defined as Q according to claim 2 provided that R^2 is other than hydrogen and is represented by C_{1-10}alkyl substituted with $N(R_6)_2$ and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, and provided that R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, with a suitable reducing agent;

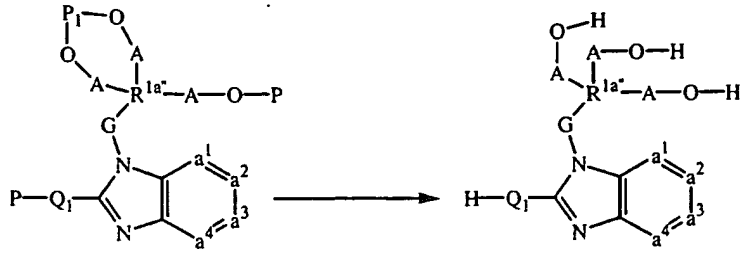
n) deprotecting an intermediate of formula (XVI), (XVI-a) or (XVI-b)



(XVI) (I'-d)



(XVI-a) (I'-d-1)

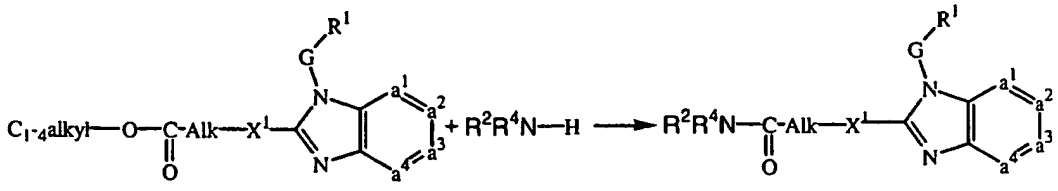


(XVI-b) (I'-d-2)

with G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 2, and H-Q_1 being defined as Q according to claim 2 provided that R^2 or at least one R^6 substituent is hydrogen,

and R^{1a}-(A-O-H)$_w$, $R^{1a'}$-(A-O-H)$_2$ and $R^{1a''}$-(A-O-H)$_3$ being defined as R^1 according to claim 2 provided that R^1 is substituted with hydroxy, hydroxyC_{1-6}alkyl, or HO(-CH_2-CH_2-O)$_n$-, with w being an integer from 1 to 4 and P or P_1 being a suitable protecting group, with a suitable acid.

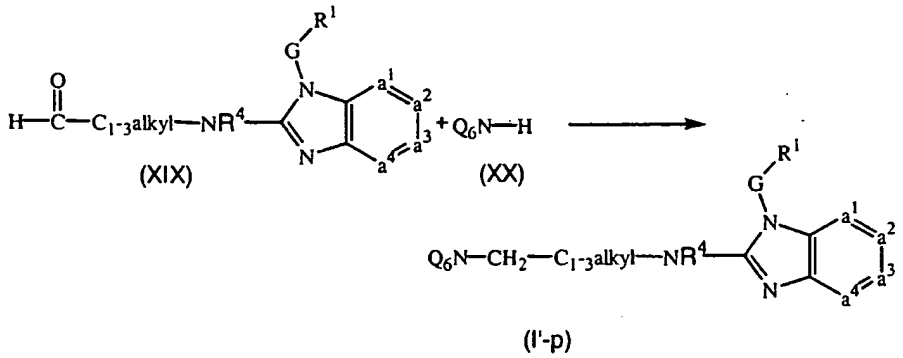
o) amination of an intermediate of formula (XVII)



(XVII) (XVIII) (I'-e)

with R^1, G, -a^1=a^2-a^3=a^4-, Alk, X^1 R^2 and R^4 defined as in claim 2, in the presence of a suitable amination agent;

p) amination of an intermediate of formula (XIX)



(XIX) (XX) (I'-p)

with R^1, G, and -a^1=a^2-a^3=a^4- defined as in claim 2, and Q_6N-CH_2-C_{1-3}alkyl-NR^4 being defined as Q according to claim 2 provided that in the definition of Q, X^2 is C_{2-4}alkyl-NR^4, in the presence of a suitable amination agent;

and, if desired, converting compounds of formula (I') into each other following art-known transformations, and further, if desired, converting the compounds of formula (I'), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and, if desired, preparing stereochemically isomeric forms, metal complexes, quaternary amines or *N*-oxide forms thereof.

16. A product containing (a) a compound as defined in claim 2 or 9, and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in the treatment or the prevention of viral infections.

17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) a compound as defined in claim 2 or 9, and (b) another antiviral compound.

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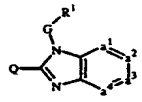
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO,

[Continued on next page]

(54) Title: RESPIRATORY SYNCYTIAL VIRUS REPLICATION INHIBITORS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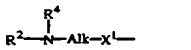
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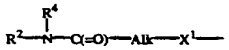
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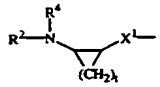
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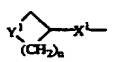
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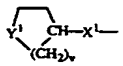
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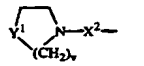
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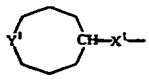
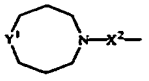

(b-7)


(b-8)

(57) Abstract: This invention concerns the use of compounds of formula (I) wherein -a^1=a^2-a^3=a^4- is a radical of formula -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N- wherein each hydrogen atom may optionally be substituted; Q is a radical of formulas (b-1), (b-2), (b-3), (b-4), (b-5), (b-6), (b-7), (b-8), G is a direct bond or C_{1-10}alkanediyl; R^1 is an optionally substituted monocyclic heterocycle; for the manufacture of a medicament for the treatment of viral infections, in particular RSV infections. Certain compounds of formula (I) are new.

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NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

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PCT/EP 00/05676

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/06 C07D471/04 C07D401/14 C07D413/14 C07D417/14
C07D405/14 A61K31/501 A61K31/4439 A61K31/454 A61K31/4184
A61K31/4188 A61P31/14 //(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2000	13/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Allard, M

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INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter ...nal Application No
PCT/EP 00/05676

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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION RELATING TO PRIORITY CLAIM

(PCT Rules 26bis.1 and 26bis.2 and Administrative Instructions, Sections 402 and 409)

To:

QUAGHEBEUR, Luc
Janssen Pharmaceutica N.V.
Patent Dept. - 3547
Turnhoutseweg 30
B-2340 Beerse
BELGIQUE

Date of mailing (day/month/year) 11 December 2000 (11.12.00)	
Applicant's or agent's file reference JAB 1499-PCT	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/05675	International filing date (day/month/year) 20 June 2000 (20.06.00)
Applicant JANSSEN PHARMACEUTICA N.V. et al	

The applicant is hereby **notified** of the following in respect of the priority claim(s) made in the international application.

1. [X] **Correction of priority claim.** In accordance with the applicant's notice received on: 30 October 2000 (30.10.00), the following priority claim has been corrected to read as follows:

EP 28 June 1999 (28.06.99) 99202088.3

[ ] even though the indication of the number of the earlier application is missing.
[ ] even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:

2. [ ] **Addition of priority claim.** In accordance with the applicant's notice received on: , the following priority claim has been added:

[ ] even though the indication of the number of the earlier application is missing.
[ ] even though the following indication in the priority claim is not the same as the corresponding indication appearing in the priority document:

3. [ ] As a **result of the correction and/or addition** of (a) priority claim(s) under items 1 and/or 2, the (earliest) priority date is:

4. [ ] **Priority claim considered not to have been made.**
[ ] The applicant failed to respond to the Invitation under Rule 26bis.2(a) (Form PCT/IB/316) within the prescribed time limit.
[ ] The applicant's notice was received after the expiration of the prescribed time limit under Rule 26bis.1(a).
[ ] The applicant's notice failed to correct the priority claim so as to comply with the requirements of Rule 4.10.
The applicant may, before the technical preparations for international publication have been completed and subject to the payment of a fee, request the International Bureau to publish, together with the international application, information concerning the priority claim. See Rule 26bis.2(c) and the PCT Applicant's Guide, Volume I, Annex B2(IB).

5. [ ] In case where **multiple priorities** have been claimed, the above item(s) relate to the following priority claim(s):

6. A copy of this notification has been sent to the receiving Office and
[X] to the International Searching Authority (where the international search report has not yet been issued).
[X] the designated Offices (which have already been notified of the receipt of the record copy).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Céline Faust
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 February 2001 (01.02.01)	
International application No. PCT/EP00/05676	**Applicant's or agent's file reference** JAB 1498-PCT
International filing date (day/month/year) 20 June 2000 (20.06.00)	**Priority date** (day/month/year) 28 June 1999 (28.06.99)
Applicant JANSSENS, Frans, Eduard et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

20 November 2000 (20.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

RECEIVED

11 JUL 2001

Patent department

PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

QUAGHEBEUR, Luc
JANSSEN PHARMACEUTICA N.V.
Turnhoutseweg 30
B-2340 Beerse
BELGIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	09.07.2001
Applicant's or agent's file reference: JAB 1498-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05676	20/06/2000	28/06/1999

Applicant
JANSSEN PHARMACEUTICA N.V.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	THORNTON, J Tel.+49 89 2399-8072

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JAB 1498-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05676	20/06/2000	28/06/1999

International Patent Classification (IPC) or national classification and IPC
C07D401/06

Applicant
JANSSEN PHARMACEUTICA N.V.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/11/2000	09.07.2001

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer
Wörth, C
Telephone No. +49 89 2399 8726

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05676

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-91 as originally filed

Claims, No.:

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 11, 12, 16, 17
	No:	Claims	2-10, 13-15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Reference is made to the following documents; they have all been cited in the written opinion:

D1: EP-A-0 099 139; 25 January 1984 (1984-01-25) cited in the application
D2: EP-A-0 144 101; 12 June 1985 (1985-06-12) cited in the application
D3: EP-A-0 145 037; 19 June 1985 (1985-06-19) cited in the application
D4: EP-A-0 151 824; 21 August 1985 (1985-08-21) cited in the application
D5: EP-A-0 151 826; 21 August 1985 (1985-08-21) cited in the application
D6: EP-A-0 232 937; 19 August 1987 (1987-08-19) cited in the application
D7: EP-A-0 295 742; 21 December 1988 (1988-12-21) cited in the application
D8: EP-A-0 297 661; 4 January 1989 (1989-01-04) cited in the application
D9: EP-A-0 307 014; 15 March 1989 (1989-03-15) cited in the application
D10: EP-A-0 393 738; 24 October 1990 (1990-10-24)
D11: EP-A-0 005 318; 14 November 1979 (1979-11-14) cited in the application
D12: WO 92 01697 A; 6 February 1992 (1992-02-06) cited in the application
D13: WO 92 01687 A; 6 February 1992 (1992-02-06) cited in the application
D14: WO 98 10764 A; 19 March 1998 (1998-03-19)
D15: EP-A-0 058 146; 18 August 1982 (1982-08-18)
D16: R.R. TIDWELL ET AL: 'Aromatic amidines : comparison of their ability to block respiratory syncytial virus induced cell fusion and to inhibit plasmin, urokinase, thrombin, and trypsin' JOURNAL OF MEDICINAL CHEMISTRY., vol. 26, no. 2, 1983, pages 294-298, XP002123605 ISSN: 0022-2623
D17: CHIBA T ET AL: 'Inhibitory effect of pyridobenzazoles on virus replication in vitro' BIOLOGICAL & PHARMACEUTICAL BULLETIN, vol. 18, no. 8, August 1995 (1995-08), pages 1081-3, XP002148491
D18: WO 9855120 A; 10 December 1998 (1998-12-10)
D19: EP 0747363 A; 11 December 1996 (1996-12-11)
D20: WO 9831363 A; 23 July 1998 (1998-05-23)

2. Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement (Reference to section V)

2.1 Novelty

2.1a *Claims 1, 11-12; 16-17*

Although the compounds of claim 1 overlap with the compounds of documents D1-D13, none of the cited documents D1-D13 discloses the use of such compounds as anti-viral agents.

Documents D14, which discloses a histamine-H1-receptor antagonist ("cetirizine", page 3, lines 10-14) as an anti-viral agent for the treatment of diseases induced by the respiratory-syncytial-virus (page 2, lines 17-22), differs from the subject-matter of the present application in sofar, as the structure of cetirizine does not possess a fused heterocyclic core.

Document D15 describes cetirizine-derivatives as anti-allergic, spasmolytic and anti-histaminic agents (page 15, line 21 - 21, line 10). However, there is no indication for the use of compounds according to claim 1 of the present application as anti-viral agents.

Document D16 describes aromatic amides and their ability to block RSV-induced cell fusion. The subject-matter of the present application differs from the compounds 1-6 of document D16 inter alia in the structure of the substituent represented by Q of general formula (I) and from the compounds 7-24 inter alia in the number of nitrogens in the core molecule.

Document D17 discloses condensed tricycles (compounds 1-13, table 1) with 2 heteroatoms (N and Y) as inhibitors on RSV replication in vitro. However, the compounds described in the present application differ from the compounds of D17 inter alia in substituent Q of general formula (I).

Documents D18-20 disclose as anti-viral compounds benzimidazoles and pyridoimidazoles, respectively. The subject-matter of the present claims 1, 11-12 and 16-17 differs from these documents in the definition of the substituent Q, in particular mainly in the terminal amino-group of (b1-4) and the terminal carbo- or heterocycle in (b4-8).

Accordingly, claim 1 meets the requirements set forth in Article 33(2) PCT.

2.1b Claims 2-10, 13-15

Documents D1-D4, D6-D7 and D11 disclose benzimidazoles or their bioisosteric analogues which are substituted at position 2 with a 4-piperidine via an amine as therapeutic compounds.

In documents D5 and D8, the benzimidazoles or bioisosteric analogues are substituted at position 2 with a 4-piperidine via methylene, oxygen, sulfur, SO or SO_2 as therapeutic compounds.

Document D9 discloses benzimidazoles and their bioisosteric analogues substituted with N-alkyl-piperazines or -1,4-diazepines as therapeutic compounds.

Documents D10 and D12-D13 describe benzimidazoles or bioisosteric analogues, substituted at position 2 with a 4-piperidine via methylene, oxygen, sulfur, SO or SO_2, which are additionally substituted at position N1 with heterocycles like furane (D10), thiazolyl and pyridinyl (D12) or oxazolyl (D13) as therapeutic compounds.

The Applicant has introduced at the end of claims 2-7 provisos, which appear to be directed to exclude the above cited prior art documents D1-D13.

However, as long as the e.g. the proviso in claim 2, line 8 in the present application is solely valid for G=methylene, the subject-matter of this claim overlaps with D4 and D6 **inter alia** for the following combinations:

present application	**D4 or D6**
-a1-a2-a3-a4- = (a-1)	-A1-A2-A3-A4- = (a-1)
G = direct bond; R^1 = pyrazinyl	R^1 = Ar^1 = pyrazinyl
Q = (b-5) with v=2 and Y^1 = NR^2	R^2 = R = hydrogen; L = (b-1)

Furthermore, the subject-matter of this claim overlaps with D7 for the same reasons as indicated for D4 and D6 in the case that G is e.g. an ethylene.

In addition, the subject-matter of the present application overlaps with the subject-matter D5 for X^1 defined as S, S=O, S(=O)2, O and CH_2, whereas the other variables are defined as described above as well as with the subject-matter of present claim 2 for the definitions given above, whereas Q is defined by (b-6) and X^2 as CH_2.

Accordingly, claims 2-10 and 13-15 do not fulfill the requirements set forth in Article 33(2) PCT.

Furthermore, as long as there is no back reference for the compounds of claim 9 (Group (I"), see description page 6, line 20 - page 7, line 37) introduced, a common structural element of this list appears to be absent.

2.2 Inventive step

Documents D18 and D20 are regarded as respected closest prior art for some of the claimed families of compounds. These documents disclose N1-C2-substituted benzimidazoles and its bioisosteric analogue pyridoimidazole as antiviral agents.

In view of these documents, the problem to be solved by the present application can be regarded as the provision of further fused 5,6-membered heterocycle-derivatives with unexpected effects.

The solution to this problem provided by the present application consists in analogisations of the C2- and N1-substituents of the benzimidazole-core or its bioisosteric analogues.

However, for the man skilled in the art, having knowledge of the combined technical teaching of

- document D16 (amidino-benzimidazoles and amidino-indole derivatives as agents exhibiting a high potency against virus-induced cell fusion and anti-viral lead compounds, see page 295, 1st col., last paragraph)),
- document D17 (fused benzimidazoles (see compounds 1-4, table 1, page 1082) as compounds exhibiting an inhibitory effect on RSV virus replication),
- documents D18-D19 (substituted benzimidazoles, which inhibit the growth of picornaviruses (see inter alia the abstracts)) and
- document D20 (substituted pyridoimidazoles - which are at present regarded as bioisoteric analogues to benzimidazoles) useful as antiviral agents,

the feature of the analogisation of benzimidazole-substituents and their isosteric analogues is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

Moreover, underlying the principles of structure-activity relationship (SAR), it is stressed that for structural similar compounds a similar biological activity can be

expected. As a consequence thereof, SAR allow to predict that for formal analogisations the pharmaceutical activity will be maintained.

Furthermore, the inhibiting effect of the well known histamine H1 receptor antagonist cetirizine on viral replication together with an inhibiting effect of RSV-induced cell modifications disclosed in document D14, page 2, lines 17-22 and page 3, lines 10-13, is a strong hint for a man skilled in the art having knowledge of the technical teaching of documents D16 and D17 (benzimidazole as lead compound for anti-viral agents) to examine, if known anti-allergic compounds bearing a benzimidazole-core exhibit also anti-viral properties, thereby arriving to the solution proposed by the present application.

It is noted, that SAR does not allow to predict whether the activity is better or worse. As a consequence thereof, an unexpected effect can be considered as an indication for inventive step. However, the applicant has not shown that the claimed compounds are likely to have any unexpected effects compared to those in the cited documents, in particular the nearest possible compounds, apparently represented by the compounds disclosed in documents D18 and D20.

As far as the scope of the claims is concerned, attention is drawn to the point, that only such compounds can be claimed which represent a solution of the problem underlying the application in suit. The extent of a reasonable generalisation depends on the credibility that substantially all the alternatives claimed must be a solution to the problem. Extremely broad generalisations e.g. like in claim 1 "optionally substituted" in the definition of the radicals (a1-5), R1 or R2 are in contradiction to the basis of even qualitative structure-activity-relationships. Taking into account the relevant state of the art and the common knowledge, it appears not to be predictable, that all alternatives would achieve the technical effect.

Accordingly, claims 1-15 do not fulfill the requirements set forth in Article 33(3) PCT.

3. **Certain observations on the international application** (Reference to section VIII)

3.1 The terms "prodrug" and "metal complex" in claim 1, 2, 8 and 9 do not fulfill the requirements of Article 6 PCT. The mere term "prodrug" is a functional expression attempting to define the subject-matter in terms of a desired property instead of indicating precisely the technical measures specifically designed to solve the problem. Functional terms will only be allowable if the solution is one which can directly be verified by tests or procedures adequately specified of known to the person skilled in the art and which verification does not need undue experimentation (cf. Guidelines C-III, 4.7). This requirement is presently not fulfilled.

3.2 It is stressed out that claims must be clear and concise in accordance to Article 6 PCT in order to enable potential users to ascertain - without undue burden - whether their planned use is likely to infringe the patent monopoly. In the present case, due to the generalisation of the claimed subject-matter of claim 2, the public has to construe 6 complicated provisos together with all the multiple structural combinations to form a valid and commercially useful opinion on whether or not a potential compound falls within the scope of the claims or not. This appears to impose a severe and totally undue burden on the public and renders the claims not clear (Article 6 PCT).

3.3 Contrary to the requirements of Rule 5.1(a)(ii) PCT, documents D10 and D14-17 are not identified and the relevant background art disclosed therein is not mentioned.

3.4 Attention is drawn to the fact that dependent claims are only admissible in the case of a allowable independent claim (cf. Rule 6.4 PCT).